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Infrared detection in flow analysis — developments and trends (review)☆

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Abstract

Flow analysis offers an inexpensive and versatile means for the automation of analytical procedures and hence it has been incorporated in many different techniques. However, the use of infrared detection in flow analysis systems is not common. Whereas Fourier transform infrared (FTIR) spectroscopic detection has been routinely used in gas chromatography (GC), its use for liquid chromatography, and now for flow analysis, flow injection analysis, or sequential injection analysis, is not frequent. The most prominent reasons are probably: (i) the strong absorption of most of the common solvents, specially water, (ii) the relative poor sensibility compared to UV–vis, fluorescence, etc. (iii) FTIR is normally not even considered a valuable detection technique, (iv) problems arising from obtaining adequate information from transient IR signals from the injected samples, and (v) only a few analytical chemist uses routinely the FTIR technique. This practice neglects that IR spectroscopy offers some unique features that now, using modern FTIR instrumentation, can be exploited in an advantageous manner. It is important to realize that each sample (analyte/matrix) represents a special and unique analytical problem; which defines the mode of operation and implementation of the IR technique. Flow analysis–IR techniques – as well as all techniques – has a number of shortcomings to solve these problems. In this article, most of these strategies such as the use of: baseline correction, derivative spectroscopy, stopped flow systems, reverse flow systems, multiparametric calibrations, etc., will be discussed. Additionally, recent developments in on-line gas phase generation–FTIR and hydride generation–FTIR spectrometry, as well as the principles of the HPLC–FTIR and capillary electrophoresis–FTIR hyphenation are also discussed. This review aims to provide an account of the state of the art, of these relatively new techniques. Its beginning, developments, applications and new trends, basically in the MID–IR, and by using transmission cells.

Keywords: Flow analysis; Infrared detection; FTIR

1. General introduction

Since its introduction by Ruzicka and Hansen in Denmarc in 1976, flow injection analysis (FIA) has been coupled to most of the spectroscopic and also to some electrochemical detection techniques. The advantages offered by the FIA systems, related to simplicity, automation, reduction in sample and reagents consumption, etc., are well established [1,2], and are the responsible of the explosive growing of the FIA coupled systems. FIA is a well-established analytical technique based on the automated injection of a series of samples in a continuous carrier stream, which offers an inexpensive and versatile means for the automation of analytical procedures, and hence it has been incorporated in many different techniques – including infrared (IR) spectrometry – mainly for quantification processes. However, the use of IR detection in flow analysis – specially in aqueous systems – is not common [3,4].

Infrared spectroscopy is a universal, versatile analytical technique for the structure elucidation of a large variety of

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organic, inorganic and biological samples. The principle of the IR spectroscopy is the measurement of the amount of IR radiation, which is absorbed (or emitted) by a sample as a function of the wavelength. The IR measurement can be carried out in the modality of transmission or reflectance, being the first one the most popular. The wavelengths of IR ranges from about 0.78–1000 μm in wavelengths (12,500–10 cm^{-1} in wavenumbers), and it is divided into a NIR infrared (12,500–4000 cm^{-1}), MID–IR (4000–100 cm^{-1}) and FAR–IR (100–10 cm^{-1}); however, the most utilized are the NIR, and specially the MID region [4–8].

IR spectroscopy has a high potential for the elucidation of molecular structures. The IR spectrum of a poly-atomic molecule is based on molecular vibrations, each specifically dependent on atomic masses, bond strengths and intra- and intermolecular interactions. As a consequence, the entire IR spectra of an organic compound provide a unique fingerprint, which can be readily distinguished from the IR-absorption pattern of other compounds including isomers. In other words, when reference spectra are available, most compounds can be unambiguously identified on the basis of their IR spectra. Moreover, characteristic absorption bands can be used for compound-specific detection. Finally, IR spectroscopy obeys a law, similar to that described by the Beer's Law, and can thus be used for quantitative purposes too. The major advantage of IR over other spectroscopic techniques is that practically all compounds show absorption (emission) and can thus be analyzed both qualitatively and quantitatively. Besides, IR spectroscopy is non destructive and admits in situ and remote measurements of almost any sample, irrespective the physical state and without elaborate preparations [4–6].

The introduction of the Fourier transform infrared (FTIR) instrumentation generated a true revolution in infrared spectrometry, due to the great advantages it provides, best known as the Coones, Fellguet, and Jacquinott advantages [7–10]. FTIR spectrometry is a fast analytical technique that provides very interesting qualitative and also quantitative information from solid, liquid and gaseous samples. At this point it is important to point out that the use of IR for quantitative purposes has grown dramatically in recent years.

The synergistic combination between FIA and FTIR developed in the last 15 years provides: (i) a simple, fast and reproducible way for loading and cleaning the IR flow cells, (ii) repeatability and accuracy, (iii) an important saving in terms of reagent and time of analysis, (iv) continuous monitoring of the spectral baseline and accurate determination of the absorption band maxima, and (v) simultaneous determination of a series of compounds in the same sample [11]. Probably, the major merits of IR detection in flow analysis systems include: easy of operating, real-time detection, and low maintenance [4–5].

Usually, FIA–FTIR is applied for single-component analysis, but since IR spectra comprise a range of absorption frequencies, multi-component analysis can be, in principle, carried out as well. Obviously, the IR absorption bands of carrier should not spectrally interfere with the marker band of each analyte. Its worthwhile to point out that modern FTIR instrumentation offers a lot of possibilities for: (i) the use of absorbance corrections, multi wavenumber calibrations, and derivative spectroscopy; which help to avoid potential interference effects, and (ii) the direct determination of various components in complex matrixes, without sample pretreatment, because it has opened up new opportunities for the resolution of mixtures and compensation for matrix interferences [12,13]. However, also non FT instruments based on light dispersion by grating of filters can be used for different applications.

In the panorama described below, it is noticeable that nowadays only few – but very productive – laboratories in the world use IR spectroscopy as a quantification technique, especially in flow systems. This fact contrasts to the big number of laboratories; that continuously and routinely use spectrophotometric, fluorimetric, atomic spectroscopic, etc., detection in their methodology developments. This fact is probably due to the reasons previously discussed. Nowadays, the flow analysis–IR techniques can be described as powerful, interesting and relatively unexplored analytical techniques, which could provide simple and adequate solutions for the analysis of a lot of complex and real samples. This article has been organized in a series of sections, which includes:

1. General introduction.
2. Antecedents and evolution.
3. The HPLC–FTIR coupling.
4. IR materials, windows, flow cells, solvents and softwares.
5. Developments and applications.
6. Current state of flow analysis–IR techniques and new trends.

This review aims to provide an account of the state of the art, of these relatively new techniques; its beginning, developments, applications and new trends; basically in the MID–IR, and by using transmission cells.

2. Antecedents and evolution

In this section some papers are described and discussed, which according to the best knowledge of the authors have fundamentally contributed in the development and evolution of the flow analysis–IR techniques.

The first precedent of the coupling between FIA and infrared spectrometry was reported by Curran and Collier [14]. The paper was entitled, "*Determination of phenyl isocyanate in a flow injection system with Infrared spectrometric detection*." The authors exposed the justification for the developing of the coupled technique as it follows: "IR spectrophotometry possessed much better selectivity than UV–vis methods. FIA techniques of sample handling are very useful for rapid and repetitive determinations. A combination of these two techniques could produce a fast, selective approach to determinations based on organic functional groups" [14]. In this work, phenyl isocyanate was used

as an organic test compound, using a variable filter-infrared spectrometer equipped with a flow through cell, and carbon tetrachloride was used as solvent and carrier. The absorption of the isocyanate moiety at 4.40 μm (2270 cm^{-1}) was monitored in a transmittance mode. However, the use of a variable filter-IR spectrometer requires that the analysis be carried out at a fixed wavelength. This condition represents a very heavy drawback when the shape of the IR band varies, and avoids the possibilities for the correction of the absorbance by means of an adequate baseline. On the other hand, the FIA–FTIR coupling was firstly reported by de la Guardia, and Gallignani in 1992: "*Flow injection–Fourier transform infrared spectrometric analysis*". In this case, the justification indicated by the authors for the developing of the FIA–FTIR coupling was: "The incorporation of the Fourier transform IR instrumentation permits the rapid recording of IR spectra in only few seconds, so it is possible to develop an adequate method for the treatment of transient signals based on the control of the spectra in an appropriate wavelengths range, which permits the accurate measurement of the baseline and the exact determination of the absorbance maximum, avoiding the undesirable use of a fixed wave number [15]. In this work, a FIA–FTIR method was developed for obtaining and storing the complete FTIR spectrum of a sample in a flowing stream as a function of time; using a simple one-channel manifold and inexpensive IR flow cells (Fig. 1A). The determination of *o*-xylene in xylol was employed as a test system, using hexane as a carrier and solvent. The absorbance of the analyte at 743 cm^{-1} was monitored in the flow system, using a baseline correction between 820 and 670 cm^{-1} (Fig. 2A). The problems related to the transient peaks were solved by means of the developing home made of a series of software. The effect of different spectroscopic and FIA parameters such as nominal resolution, flow rate, internal

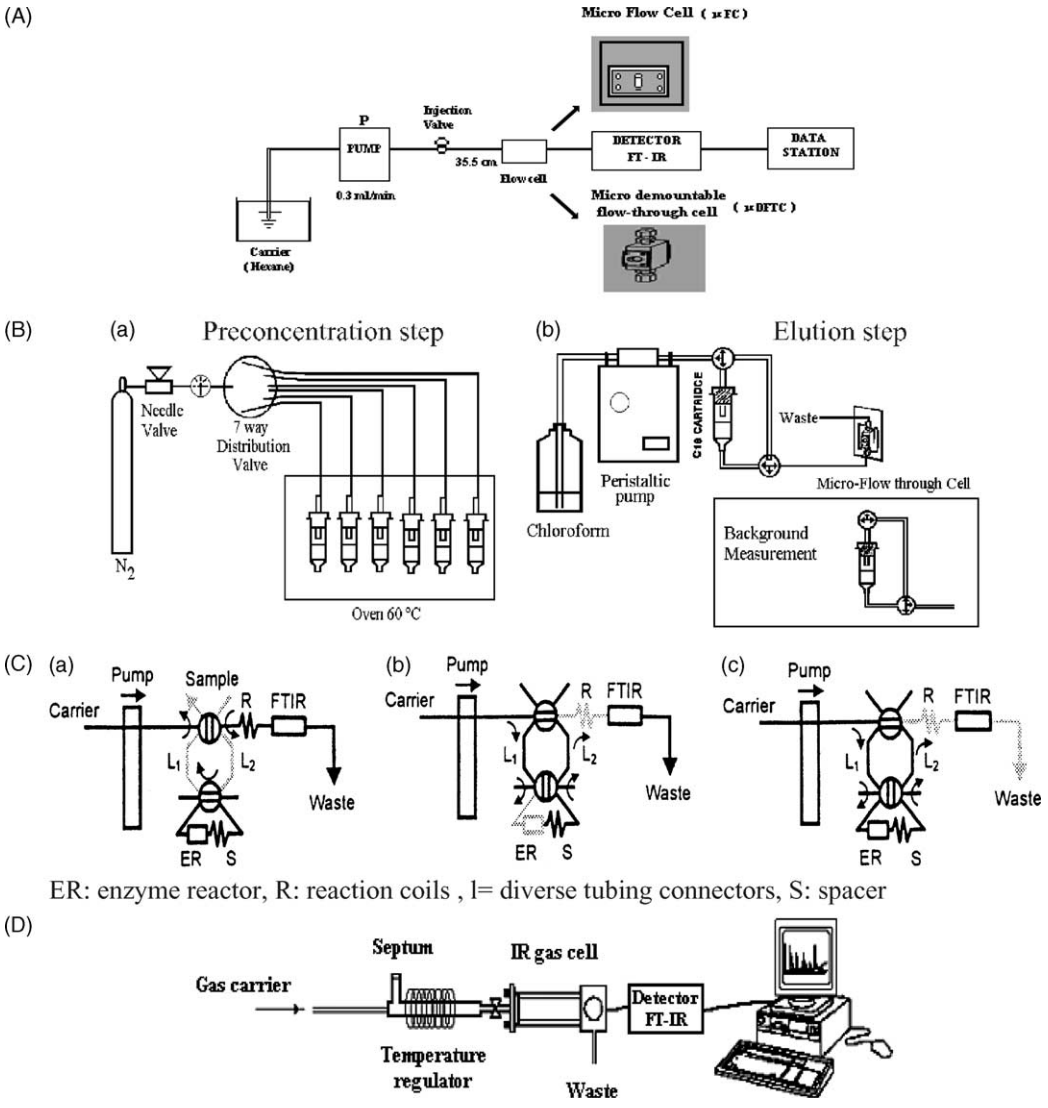


Fig. 1. Different manifolds used in flow analysis–FTIR. (A) One channel manifold used for the determination of *o*-xylene in xylol [15,17]. (B) Manifold used for the determination of carbaryl in waters, using SPE pre-concentration [16]. (C) Manifold used for the determination of sucrose in aqueous matrixes based on the enzymatic cleavage of sucrose in α-D glucose and β-D glucose [29]. (D) Manifold used for the on-line vapor phase generation–FTIR [49].

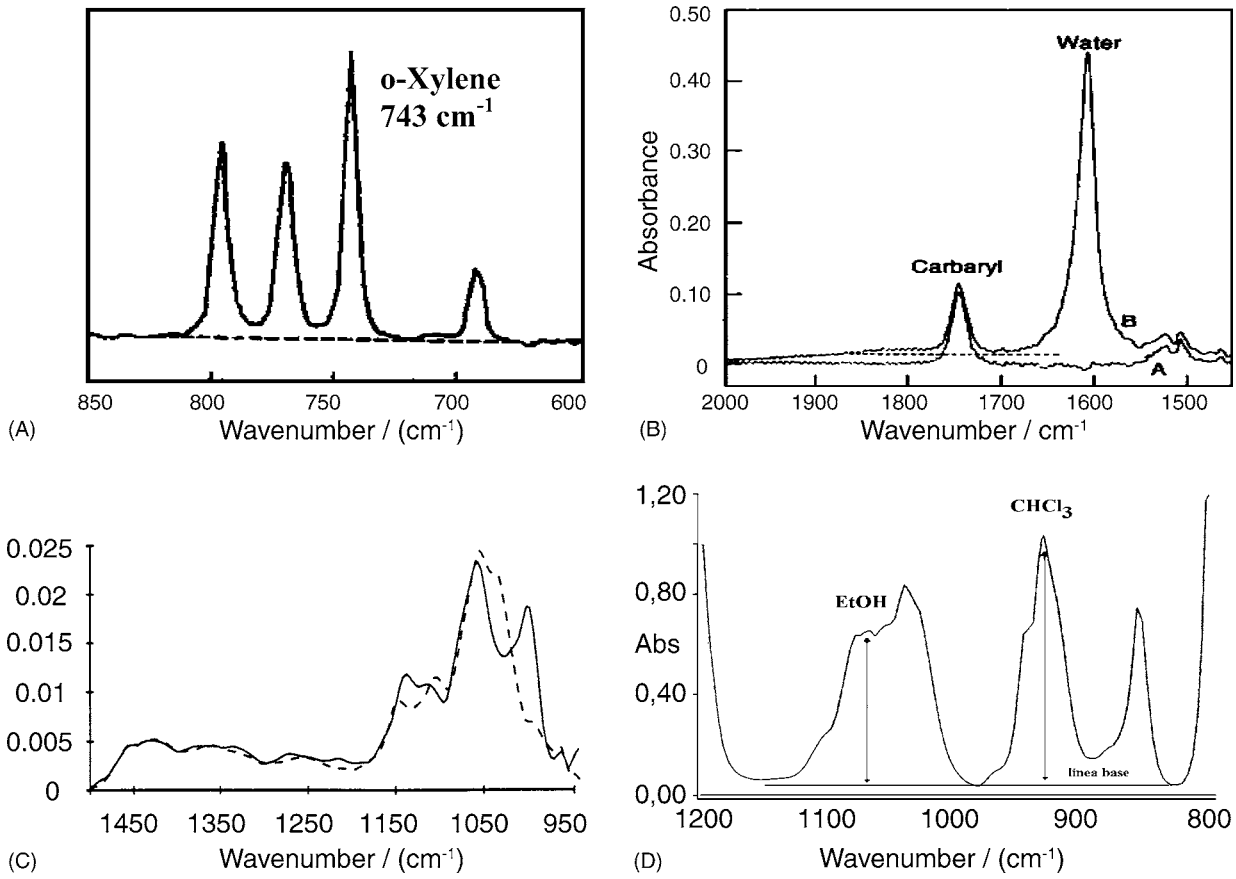


Fig. 2. Absorption FTIR spectra. (A) Xylol in hexane [15,17], (B) carbaryl in CH_2Cl_2 [16], (C) sucrose before (- - - -) and after (—) the enzymatic cleavage (sucrose → α-D glucose + β-D glucose) [29], (D) ethanol 1% (v/v) in $CHCl_3$ (gas phase) [49].

volume cell, and the injection volume on the transient signals, and in the figures of merit, was extensively studied. In a further study in 1994, the incorporation of an analyte enrichment step – by means of solid phase extraction (SPE) – was proposed to improve the analytical sensitivity, and then the detection limit in the FIA–FTIR spectrometric analysis. The paper was entitled "*On-line preconcentration and FTIR determination of carbaryl*" [16]. The pre-concentration step was carried out by trapping the analyte on a SPE. After drying of the cartridge, with dried nitrogen gas, the analyte was eluted with dichloromethane, and detected by IR transmission spectroscopy (Fig. 1B). Absorbance measurements were carried out at the carbonyl band (at 1746 cm^{-1}), using a horizontal baseline established at 1875 cm^{-1} (Fig. 2B).

The FIA–FTIR technique was successively applied to the determination of diverse analytes in different matrixes such as solvents [15,17] gasoline [13,18–20], pharmaceuticals [21–23], pesticides [16,24], alcoholic beverages [25,26], soft drinks [27,28], etc.

On the other hand, until 1994 Kellner†, Lendl et al. of the University of Vienna, Austria, reported interesting contributions in FTIR spectroscopy. In 1995 they published a paper entitled, "*Flow analysis determination of sucrose by flow injection analysis with Fourier transform infrared detection*" [29]. In this work, the researchers proposed a new methodology for the determination of sucrose in complex aqueous matrices by FIA with FTIR detection, based on the enzymatic cleavage of sucrose by means of invertase to α-D glucose and β-D glucose. A special manifold consisting of two internally coupled injection valves being switched simultaneously was applied to facilitate recording FTIR spectra of the sample before and after the enzymatic reaction (Fig. 1C). The analytical readout was taken from the different spectra obtained by subtracting the FTIR spectra of the sample before and after the reaction (Fig. 2C). Other interesting contributions of this group related to FTIR spectrometry are: the use of a quantum cascade laser as a light source in the MID–IR [30], the quantification of metal ions in aqueous solutions by means of the use of ion exchanger beads [31], the use of flow through sensors for enhancing the sensibility and selectivity of determinations in aqueous media [32], different applications in clinical chemistry [33–35], the determination of enzymatic activity [34–40], different FIA and SIA designs, specially for the determination of sugars [39–46], different approaches for automated multivariable calibration in SIA systems [45,46], and the liquid chromatograpy (HPLC)-FTIR hybridization for the determination of sugars and organic acid in different matrixes [47,48].

In the last 8 years, until 1995, developments proposed by the Miguel de la Guardia group [49–62] in vapor phase

generation–FTIR spectrometry (indicated in the text as on-line-VPG–FTIR), based on the on-line generation of vapor phases from liquid and solid samples, by means of the simple sample volatilization or a chemical reaction, have improved direct determination by FTIR due to the high transparency of gases, the low background values achieved and the possibilities offered by using multiple-pass cells to increase the analytical sensitivity. The first paper (1995) was entitled "*Vapor generation–Fourier transform infrared spectrometry. A new analytical technique*" [49]. In this work, the determination of ethanol in commercial chloroform was carried out using a single-channel manifold with a nitrogen carrier flow (see Fig. 1D). The absorbance ratio between the ethanol and chloroform bands at 1066 and 931 cm^{-1}, respectively, – both corrected by the absorbance at 835 cm^{-1} – was selected as the measurement criterion (Fig. 2D). The effect of different FIA and spectroscopic parameters of the system on the quality of the analytical signal, and then, in the figures of merit, was extensively studied. The on-line-VPG–FTIR technique was successfully applied to the analysis of solvents [50,51], alcohols in different matrixes, such as alcoholic beverages, cosmetics [52–54], and blood [55], and for the analysis of gasoline [56], SO_2 in must and wines [61], and pesticides [62]. On the other hand, the idea of the vapour generation by means of an on-line chemical reaction was initially tested for the analysis of carbonate in waters and solid samples [57–60]. In this case, the different chemical forms of carbonate (carbonate, or acid carbonate) were transformed into gaseous CO_2 by means of the on-line acidification of the sample. Most recently, in 2002, the flow analysis–hydride generation (HG)–FTIR spectrometry coupling, developed by Gallignani et al. [63–65] opens an alternative and elegant way for the determination of some hydride forming elements. The initial work was entitled "*Flow analysis–hydride generation–Fourier transform infrared spectrometry. A new analytical technique for the individual and simultaneous determination of antimony, arsenic and tin*" [63]. The researchers used a continuous flow manifold for the HG generation, and a FTIR spectrometer as a detector (Fig. 3a). The gaseous analyte hydrides ($M_nH_{m(g)}$) generated, were transported by means of a gas carrier stream inside the IR gas cell and the corresponding FTIR spectra were acquired in a continuous mode. Fig. 3b presents the FTIR absorption spectra of the stibine (SbH_3), arsine (AsH_3), and stannane (SnH_4). This hy-

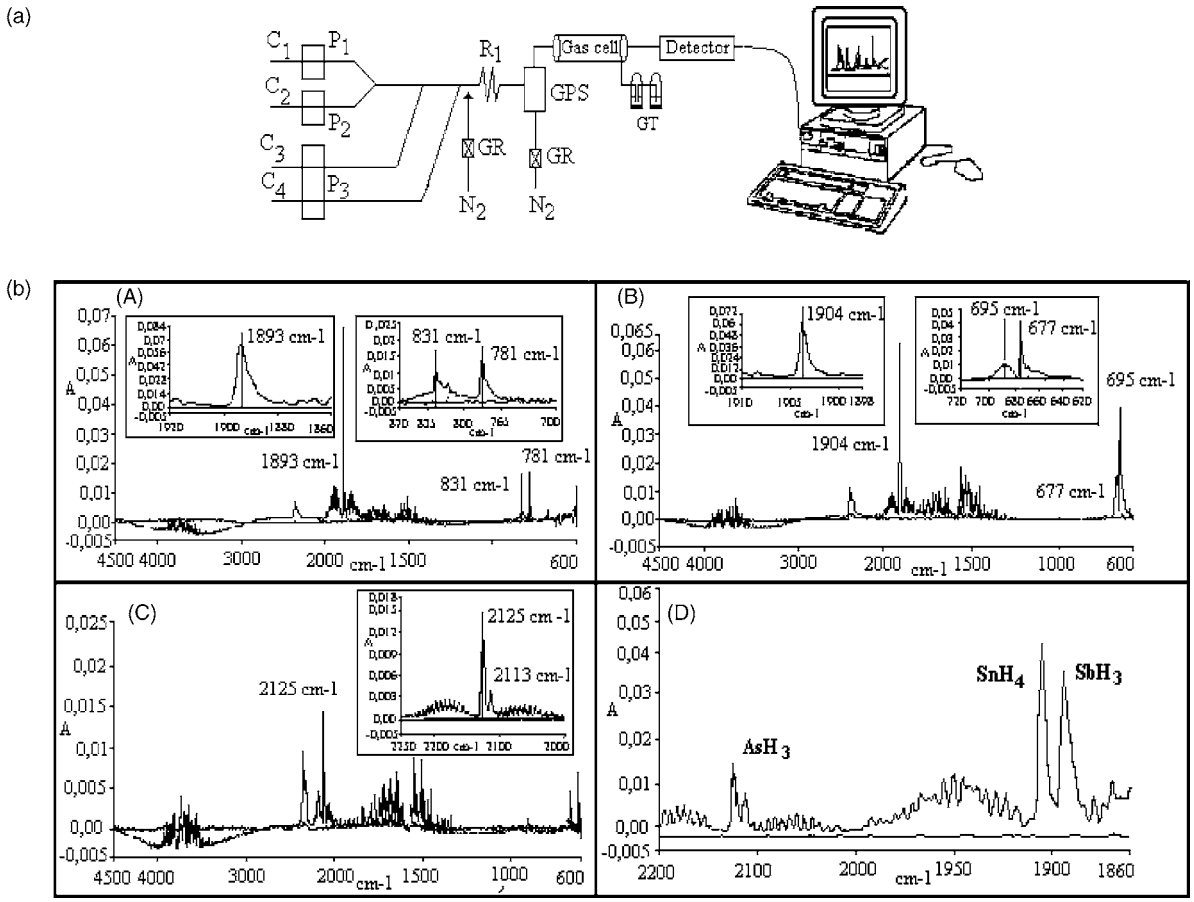


Fig. 3. Flow analysis–HG–FTIR. (a) Manifold used for the flow analysis–HG–FTIR coupling. P_1–P_3: peristaltic pumps (time based injection system), R_1: reaction coil, GPS: gas phase separator, GT: gas trapping, C_1: sample, C_2: carrier (water), C_3: acid channel, C_4: $NaBH_4$ solution. (b) FTIR spectra of: stibine (A—SbH_3), stannane (B—SnH_4), and arsine (C—AsH_3). Parts (B–D) corresponds to a FTIR spectrum obtained from a solution containing arsenic, antimony and tin (10 mg l^{-1} of each one) [63].

bridized system enhanced the analytical potentialities of the FTIR instrumentation, and the analytical advantages offered by the HG and flow analysis techniques. The novel analytical technique was immediately applied to the determination of antimony in pharmaceuticals such as glucantime [64,65].

3. The HPLC–FTIR coupling

The HPLC–FTIR coupling is not the aim of this work; however, its growth and developing in recent years has to be pointed out [3,4,66–75]. The similarities between FIA–FTIR and HPLC–FTIR are evident. For this reason, it is worthwhile to point out the real similarities and differences between both coupled techniques. In principle, the term flow analysis can be used to provide a common cover for both, liquid chromatography (LC) and FIA, because both techniques are based on the injection of a sample plug into a flowing stream, passed through a modulator and recording of a transient peak [3,4]. However, the processes that are carried out in the modulator are different; transport and chemical reaction in FIA, and separation and transport in LC. However, the same interfaces can be used for a FTIR spectrometer as a detector [4]. The interfaces can be divided into two categories: flow through cells, where the liquid is probed directly, and solvent removal interfaces, where the analyte is separated from the carrier prior the detection. The first approach is the simplest, and can be used in both techniques. The effluent from the LC column – or the carrier in a FIA system – is passed through the flow cell, while the FTIR spectra are continuously acquired. The merits of the flow cell IR approach are: easy of operation, real-time detection, and low maintenance; but its main drawback lies in the significant absorption in the IR region of the solvents commonly used [4]. This absorption seriously limits both the analytical sensitivity and the obtainable spectral information [3].

On the other hand, in the second approach used in LC/HPLC–FTIR, an interface is used for the solvent evaporation, and the separated compounds are deposited onto a substrate suitable for the IR detection. The major advantages of the solvent elimination approach are: (i) the possibility to obtain full spectra of the analytes, and (ii) a considerable enhanced sensibility. However, the characteristic of the solvents commonly used limits its application again, because aqueous eluents are not easily eliminated, and thus the evaporation interfaces are often rather complexes [4]. The articles of Schindler and Lendl [3], Somsen and Visser [4], and Somsen et al. [5] review the developments, practical aspects, the current status and the state of the art of this interesting coupled technique “LC/HPLC–FTIR”, covering both coupling approaches.

In the same way that HPLC, capillary chromatography (CE) is a powerful separation technique, and hence it has been received much attention in the later years. CE is an electrically driven separation technique for the analysis of ionized and partially ionized species, which in most cases is carried out in aqueous solutions. Advantages of CE are the high efficiency of separation combined with short analysis times and remarkably low injection volumes. Detection in CE is a challenge due to the small inner diameter of the capillaries used. The most common detection used is UV, but also other systems have been used such as laser induced fluorescence, mass spectrometry, and recently also FTIR spectrometry. On-line FTIR detection in CE implies certain difficulties, since fuse silica – the capillary material – and water from the separation electrolyte are strong IR absorbents. To overcome the problem of the total IR absorption by the fused silica, the working group of “Analytical Chemistry and Vibrational Spectroscopy” of Vienna developed a micromachined IR flow through cell [78–80]. The cell is a sandwich construction of highly transparent CaF_2 windows and epoxy polymer forming a flow through channel with a width of 150 μm and a height of 15 μm where the IR beam passes perpendicular to the flow direction [76–78]. Other solutions for the CE–FTIR interface consist in micromachining and enclosing capillaries in CaF_2 [79], the use of glass microconcentric nebulizers [80], etc. The articles of M. Kölhed et al. [77,78] review the principles, developments and practical aspects of this interesting coupled technique “CE–FTIR”.

4. IR materials, windows, flow cells, solvents and softwares

Nowadays, different IR material, windows, IR flow cells, kinetic softwares, multiparametric softwares, and very speedy FTIR instrumentation are commercially available, which greatly facilitate the use of IR detection in flow analysis systems. Concerning to the IR optical material, Table 1 presents the optical and physical characteristics of the most commonly used IR material windows, and the required precautions. The choice for a specific window material is mainly determined by the properties of the carrier, the solvent, and the spectral region that has to be monitored. A variety of transmission flow cells, differing in design, optical material, pathlength and internal volume are commercially available. The selection of the flow cell usually is a compromise between availability, cost, pathlength, and internal volume. In general, the minimum internal volume of the flow cell is preferred, in order to avoid dilution processes. However, concerning the pathlength, its selection is a compromise between sensibility and the solvent transparency. According to the dependence between the absorbance and the optical pathway, type Beer’s law, the absorbance increase with the pathlength. However, extending this parameter, it also results in an increase in the carrier and solvent absorption [4,5]. Thus, a compromise selection is required. Different designs and types of transmission IR flow cells for liquid samples are commercialized. Fig. 4 shows the classical transmission cells, with circular and rectangular geometries, respectively. This type of transmission cells can be used as flow cells, but using low flow rates. In this case, the optical body of the cells, consist in two

Table 1
Optical materials for use in IR flow cells

Material	Spectral transparency (cm^{-1})	Solubility in water (g/100 ml)	Precautions attacked by
KBr	40,000–400	Very soluble — 53.5	H_2O, lower alcohols
NaCl	40,000–625	Very soluble — 35.7	H_2O, lower alcohols
CsI	40,000–200	Very soluble — 44.4	H_2O, lower alcohols
KRS-5	20,000–250	Slightly soluble — 0.05	Complexing agents
AgCl	25,000–360	0.00015	Complexing agents
Quartz	25,000–2500	Insoluble	Hot H_2SO_4, aq. regia
Polyethylene	625–33	Insoluble	Chlorinated solvents
AMTIR	11,000–725	Insoluble	Alkalis
BaF_2	50,000–740	Insoluble	NH_4^+, acids, salts
CaF_2	50,000–1.110	Insoluble	NH_4^+, acids, salts
CdTe	20,000–360	Insoluble	Acids, HNO_3
Ge	5500–600	Insoluble	Hot H_2SO_4, aq. regia
Si	8300–660 360–70	Insoluble	HF, HNO_3
ZnS	17,000–720	Insoluble	Acids
ZnSe	20,000–454	Insoluble	Acids, strong alkalis, amines

IR transparent windows, one of them drilled, and the other one un-drilled, which are separated by a spacer. The optical set of the cell is supported into a metal body, and is protected by means of neoprene or Teflon gaskets. The metallic support is drilled too, in its upper and down body, in the same position that the drilled window and the spacer. These perforations are connected with capillary tubes for the entry and exit of the carrier solution. The major disadvantages of this type of transmission cells are the dimension of the windows (typical values are 32 mm × 2 mm; and 39 mm × 18 mm × 2 mm for the circular and rectangular geometries, respectively) and as a consequence a relatively great dead volume. However, nowadays, different transmission micro flow cells, based in these geometries, but with lower dimensions and dead volume, are commercially available. On the other hand, Fig. 4B depicted the principle of two typical micro flow cells. The basic part of the cell consists of an IR-transparent cavity (Fig. 4B-a: transmission cavity flow cell), or two circular IR-transparent windows, separated by two semicircular metal spacers (Fig. 4B-b: micro flow through cell). The optical set is mounted into a metal body between flexible rings to prevent breakage, and the carrier enters and exits the cell via capillary tubes connected to an assembly of universal fitting. The IR beam passes perpendicularly through the carrier flow. This kind of flow cells was originally designed for the liquid chromatography-IR coupling; but obviously can be used in a continuous flow pattern. Additional equipment can be purchased for operation at elevated temperature and pressure [3]. The main disadvantage of the cavity flow cells is that a special and unique drilled cavity cell is required for each material–pathlength pair selected for the experimental work. Additional information about this and other types of transmission flow IR cells can be found in the corresponding catalogues.

As has been previously mentioned, probably the major drawback of the flow-cell FTIR choice is the significant IR absorption of the solvents commonly used, especially water. Fig. 5 shows the IR absorption spectra – and the corresponding spectral transparency regions – of four of the most frequently used solvents: water, and a series of organic solvents such as CCl_4, $CHCl_3$, and hexane. The strong water absorption in the IR region is well documented [25–26]. Nevertheless, when very small pathlengths are used (<0.05 mm), two very interesting transparency regions appear in the intervals between 2800 and 1900 and 1500 and 900 cm^{-1} (Fig. 5A). The second one is of great interest, since the absorption bands, characteristic of the C–O link, appear in this region. These conditions allow performing the alcohols [25,26] and sugars analysis in aqueous media [24,25,29,41–44]. As an example, Fig. 2C shows the FTIR spectrum of a 50 g sucrose l^{-1} in aqueous medium. On their account, organic solvents present a much bigger transparency in the MID infrared, (Fig. 5B–D), allowing, in some cases, the use of pathlengths cells of several millimetres [6–8]. At this point it is important to point out that, the problems previously described, related to the solvent absorption, represent a very heavy drawback basically in liquid phases. In contrast, the backgrounds achieved in vapour phases are generally very clean, because the gases that are generally used in processes such as transport, sweep, dragging or stripping (N_2, O_2, H_2, Ar, etc.) are not active in the infrared region.

For the vapour phase, two types of commercialized available cells can be distinguished. The first one corresponds to the classical and standard IR gas cells (Fig. 6A). It basically consists in a hollow cylindrical body, which includes an inlet and outlet for the continuous flow of the gas carrier; and two demountable circular windows, at the beginning and ending of the body. The maintenance and cleaning of this type of cells is very easy. Probably, its major disadvantage is that it has a high dead volume. For example, the internal volume of a typical cell with 10 cm of pathlength, equipped with 32 mm circular windows, is approximately of 60 ml.

The second type of IR gas cells corresponds to the multiple pass cells (Fig. 6B); which are characterized by

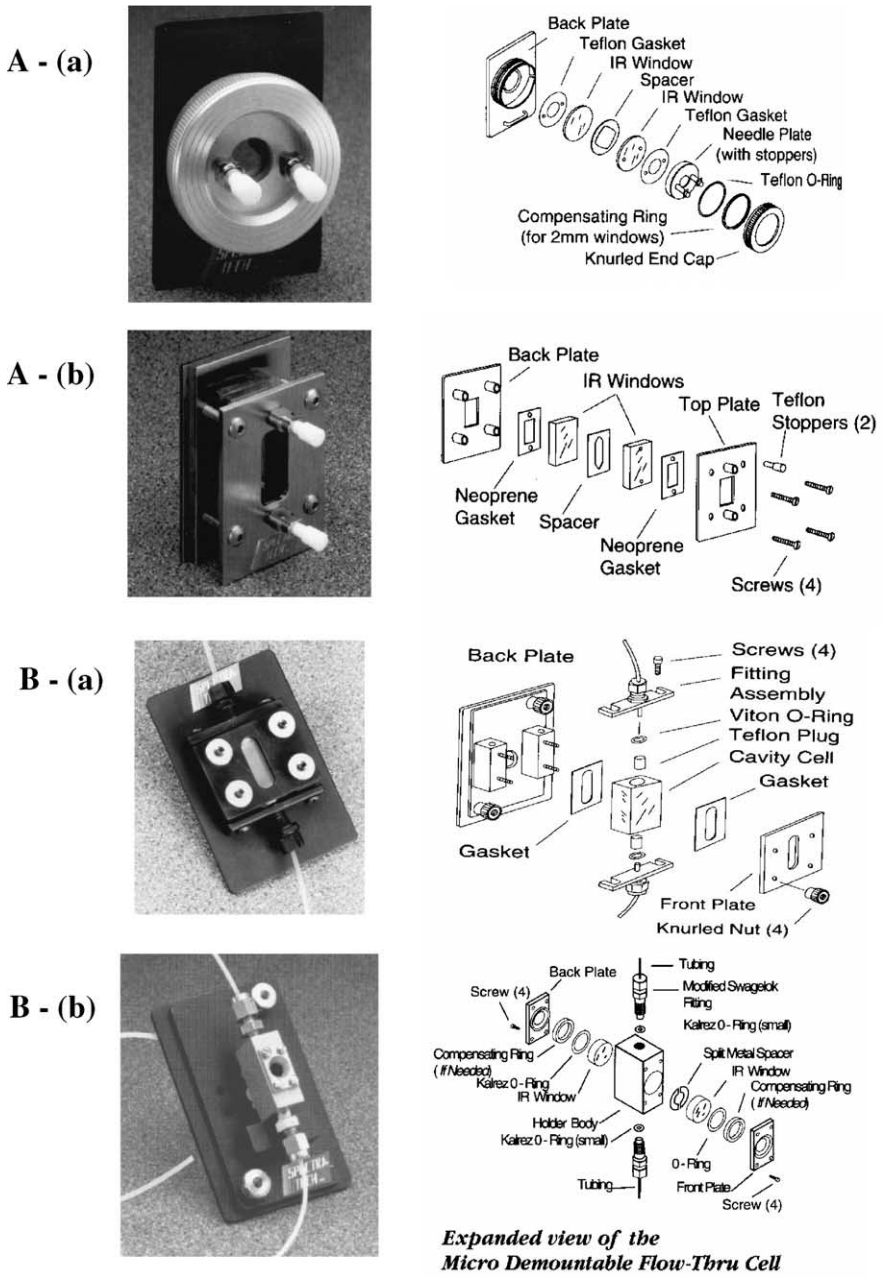


Fig. 4. Transmission IR flow cells. (A) Standard transmission cells: (a) circular geometry, and (b) rectangular geometry. (B) Micro flow cells: (a) transmission cavity flow cell, (b) demountable micro flow through cell.

very high pathlengths (various meters). This condition permits an important enhance in the analytical sensitivity of the systems. The major disadvantage of these cells is that they are very expensive. On the other hand, some experimental precautions have to be considered in order to protect the internal mirrors of the cell. Nowadays, an interesting variety of this kind of cells is available, with different pathlengths (up to 10 m), internal volumes and prices. More information about this kind of gas cells (principles, components, geometry, path-lengths, internal volume, windows availability, etc.) can be found in the corresponding catalogues.

Finally, concerning the softwares required for the developing of the FIA–FTIR coupling, all the FTIR spectrometer producers have developed kinetic softwares, which permit the easy and adequate acquisition – and treatment – of the data obtained in continuous flow systems.

5. Developments and applications

In this section, about 100 papers about methodological developments using IR detection in flow analysis systems that have appeared in the last 15 years, are mentioned or

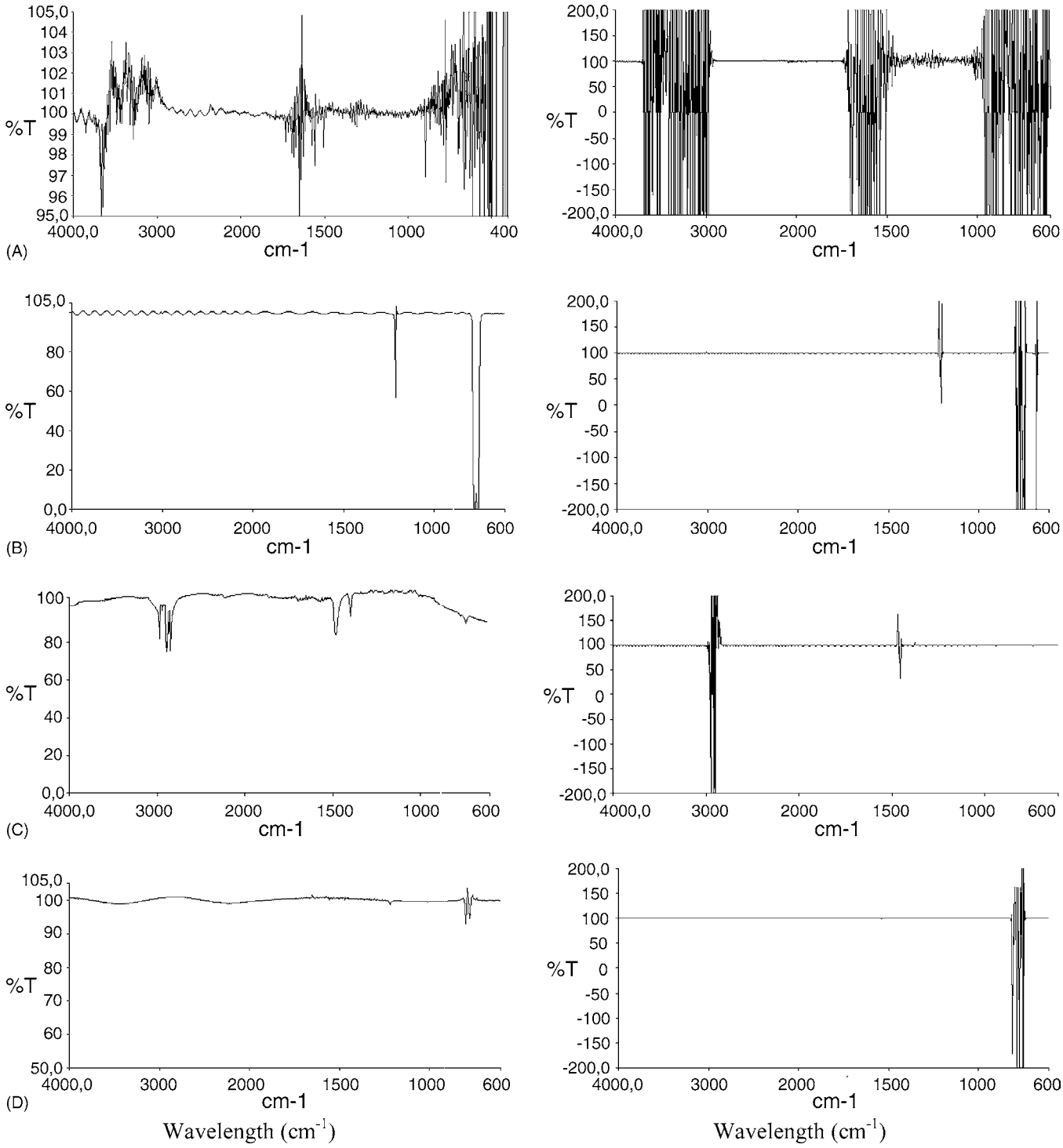


Fig. 5. Absorption FTIR spectra – and the corresponding transparency regions – of different solvents in the MID–IR region. (A) Water, (B) pure chloroform ($CHCl_3$), (C) pure hexane (C_6H_{14}), and (D) pure carbon tetrachloride (CCl_4). Experimental conditions: pathlength: 0.1 mm, ZnZe windows, 25 scans.

described. These works have been grouped – for convenience – in some cases over the base of the matrix (organic solvents, gasoline, pharmaceutical products and pesticides) and in other cases over the analyte base (alcohols, sugars, and anions). At this point, it is important to realise, that each sample (analyte/matrix) represents a special and unique analytical problem; which defines the mode of operation and implementation of the IR technique. Flow analysis–IR techniques – as well as all techniques – has a number of shortcomings to solve these problems. In this section, most of these strategies will be discussed.

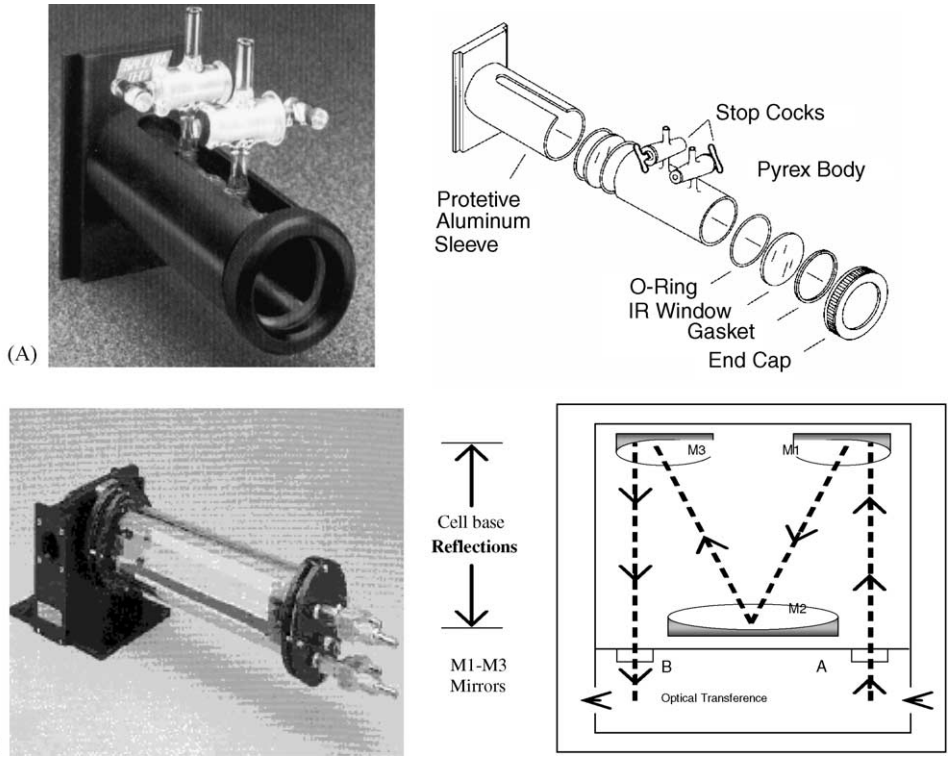


Fig. 6. IR gas cells. (A) Standard short pathway IR gas cell (pathlength = 10 cm). (B) Multiple pass IR gas cell.

5.1. Solvents

Garrigues et al. [17] reported a simple FIA–FTIR procedure for the simultaneous determination of *o*-xylene, *p*-xylene, and *m*-xylene in xylol samples, using hexane as solvent and carrier [17]. The absorbance measurements of the three isomers, corrected by a common baseline established between 820 and 695 cm^{-1}, were carried out at 743, 770, and 796 cm^{-1}; respectively (see Fig. 2A). On the other hand, Garrigues et al. and López-Anreus et al. described simple and direct FIA procedures for the determination of water in organic solvents such as dichloromethane and methyl isobutyl ketone (MIBK) [81], and ethanol in chloroform samples [82], respectively; based on the measurement of the OH stretch of water and ethanol in the near infrared region. Table 2 summarizes the experimental conditions of the methods presented. López-Anreus et al. [49] used the on-line-VPG–FTIR technique for the resolution of a toluene/MIBK mixture [49], and for the analysis of paint solvents containing butyl acetate, toluene and MIBK [50]. In this work, the quantification of the three components was carried out using the corrected integrated absorbance – obtained from the transient signals – between 1074 and 1070 cm^{-1}, 731 and 727, 731 and 727 cm^{-1}, respectively. The determination was also carried out using the pleast least squares (PLS) calibration method.

5.2. Gasoline

The determination of aromatic hydrocarbons compounds such as benzene, toluene, etc., and additives such as methyl *tert*-butyl ether (MTBE), is necessary in several areas of the petroleum, petrochemical and related industries. FIA–FTIR can provide simple and automated methods for these analyses. Gallignani et al. developed an automated FIA–FTIR procedure for the determination of benzene in gasoline [18]. The method, based on the injection of gasoline samples – diluted (1 + 9) in hexane – into a hexane carrier, permits the direct determination of benzene without any special pre-treatment of samples, monitoring the absorbance at 675 cm^{-1}. The strong interfering effect of toluene was easily eliminated, correcting the benzene absorbance by means of a baseline established between 712 and 650 cm^{-1}, or by using the peak to valley of the first order derivative spectra. Additionally, a rapid quality control procedure was suggested, based on the on-line injection of gasoline samples – diluted in hexane – into a carrier stream of 0.5% (v/v) benzene in hexane.

The determination of MTBE was carried out by means similar procedures, using the peak to valley (1209–1201 cm^{-1}) measurement of the first order derivative spectra at the 1205 cm^{-1} band [13,20]. Concerning the toluene analysis, a comparative study of different approaches for its determination in gasoline was carried out, including the use of different analytical bands and derivative strategies [19]. The

Table 2
Experimental conditions of different flow analysis–IR methods developed for the analysis of organic solvents and gasoline

Sample	Analyte	Measurement criterion[a]	Technique mode	Carrier-flow rate injection volume	IR cell[b] b (mm)	Reference
Xylol	*o*-Xylene	A*c: 743 cm^{-1} BLc: 820 and 670 cm^{-1}	FIA–FTIR	Hexane 0.27 ml min^{-1}	TFC-(KBr) 0.13 mm	[17]
	m-Xylene	A*c: 770 cm^{-1} BLc: 820 and 670 cm^{-1}		200 μl		
	p-Xylene	Ac: 796 cm^{-1} BLc: 820 and 670 cm^{-1}				
Dichloromethane (CH_2Cl_2)	Water (H_2O)	A^*: 1898 nm	FIA–NIR[c]	Dried CH_2Cl_2 1.5 ml min^{-1} 200 μl	SFC-(quartz) 10 mm	[81]
Metyl isobutyl ketone (MIBK)	Water (H_2O)	A^*: 1907 nm	FIA–NIR[c]	Dried MIBK 1.5 ml min^{-1} 200 μl	SFC-(quartz) 10 mm	[81]
Chloroform ($CHCl_3$)	Ethanol CH_3CH_2OH	A^*: 2272 nm	FIA–NIR[c]	Dried $CHCl_3$ stabilized with amylene 1.5 ml min^{-1} 100 μl	SC-(quartz) 10 mm	[82]
Gasoline	Benzene	A*c: 675 cm^{-1} BLc: 712–650 cm^{-1}	FIA–FTIR	Hexane 0.28 ml min^{-1}	TFC-(KBr) 0.12 mm	[18]
Gasoline	MTBE	1D: 1205 cm^{-1} $(P–V)_v$: 1209–1201 cm^{-1}	FIA–FTIR (derivative)	Hexane 0.28 ml min^{-1}	TFC-(KBr) 0.12 mm	[13]
Gasoline	Toluene	A*c: 728 cm^{-1} BLc = 835–575 cm^{-1} 1D: 728 cm^{-1} $(P–V)_v$: 731–725 cm^{-1}	FIA–FTIR (derivative)	Hexane 0.28 ml min^{-1}	TFC-(KBr) 0.12 mm	[19]
Gasoline	Benzene	1D: 675 cm^{-1} $(P–V)_v$: 678–672 cm^{-1}	FIA–FTIR (derivative) (simultaneous)	Hexane 0.28 ml min^{-1}	TFC-(KBr) 0.12 mm	[20]
	MTBE	1D: 675 cm^{-1} $(P–V)_v$: 678–672 cm^{-1}				
	Toluene	1D: 728 cm^{-1} $(P–V)_v$: 731–725 cm^{-1}				

[a] Measurement criterion: A^* = absorbance at the maximum absorption band; A*c = corrected absorbance; BLc = baseline correction; 1D: first order derivative spectrum at the analytical band; $(P–V)_v$: peak to valley measurement.
[b] IR cell: TFC = transmission IR flow cell-(windows material); b = pathlength. SFC = classical (standard) flow cell.
[c] FIA–NIR: In these methods, the dried solvent and methanol stabilized with amylene, respectively, were used as carrier and reference (for the double beam spectrophotometric system).

experimental conditions of the previously described methods are summarized in Table 2. In a further study, and based in the acquired information on the matrix gasoline, the researchers proposed a simple way for the simultaneous determination of benzene, toluene and MTBE [20]. The same analysis was carried out by means of the on line–VPG–FTIR technique [56]. In this case, the flow injection recordings obtained for the IR bands between 671 and 675, 727 and 731, and 1210 and 1214 cm^{-1} were employed for the determination of benzene, toluene and MTBE, respectively. On the other hand, the information offered by the FTIR spectrum (4000–600 cm^{-1}) of kerosene (the fuel used for civil and military jet-fuel turbines) obtained in a stopped flow mode, has been used – by means multivariate calibrations – for prediction of the fuel properties such as: density, freezing point, flash point, aromatic content, initial and final boiling point, and viscosity [83]. Recently, a similar development was carried out by Gomez-Carracolo et al., based in vapour phase generation–FTIR spectrometry [84].

5.3. Pharmaceuticals

Infrared spectroscopy has been extensively used for the quality control analysis of the “raw material” in the pharma-

Table 3
Experimental conditions of different flow analysis–IR methods developed for the determination of active principles in pharmaceuticals

Sample	Analyte	Measurement criterion[a]	Technique mode	Carrier-flow rate Injection volume	IR cell[b] *b* (mm)	Reference
Pharmaceuticals (commercial formulation)	Ibuprofen	A*c: 1710 cm^{-1} BLc: 1785–1650 cm^{-1}	FIA–FTIR	CCl_4 0.28 ml min^{-1} 320 μl	TFC-(KBr) 0.10 mm	[21]
Pharmaceuticals (commercial formulation)	Acetyl salicilic acid	A*c: 1770 cm^{-1} BLc: 1900–1537 cm^{-1}	FIA–FTIR (simultaneous) and reverse flow	CH_2Cl_2 0.81 ml min^{-1}	TFC-(KBr) 0.117 mm	[22]
	Caffeine	A*c: 1661 cm^{-1} BLc: 1900–1537 cm^{-1}		300 μl		
Pharmaceuticals (commercial formulation)	Paracetamol	A*c: 1515 cm^{-1} BLc: 1900 cm^{-1}	FIA–FTIR	Ethanol 10% (v/v) in CH_2Cl_2 0.97 ml min^{-1} 400 μl	TFC-(KBr) 0.17 mm	[23]
Pharmaceuticals (commercial formulation)	Paracetamol	A*c: 1274 cm^{-1} BLc: 1239–1309 cm^{-1} Ac: 1498 cm^{-1} BLc: 1479–1518 cm^{-1}	FIA–FTIR	Water 2.19 ml min^{-1} 500 μl	MCC*	[85]
Pharmaceuticals (commercial formulation)	Propyl-phenazone	A*c: 1595 cm^{-1}. BLc: 2000–890 cm^{-1}	FIA–FTIR	$CHCl_3$	TFC-(KBr) 0.178 mm	[87]
	Caffeine	1D: Peak at 1712 cm^{-1}				
Pharmaceuticals (commercial formulation)	Ketoprofen	A*c: 1712 cm^{-1} BLc: 1793–1540 cm^{-1} Ac: 1666 cm^{-1} BLc: 1793–1540 cm^{-1}	FIA–FTIR	CCl_4 0.92 ml min^{-1} 500 μl.	TFC-(KBr) 0.178 mm	[88]
Pharmaceuticals (glucantime)	Antimony Total Sb	1D: 1893 cm^{-1} $(P–W)_v$: 1891–1895 cm^{-1}	On line-HG–FTIR	Water Continuous	IR gas cell 0 cm	[64]

[a] Measurement criterion: *A** = absorbance at the maximum absorption band; A*c = corrected absorbance; BLc = baseline correction; 1D: first order derivative spectrum at the analytical band; $(P–V)_v$: peak to valley measurement.
[b] IR cell: TFC = transmission flow cell-(windows material); MCC: microcircle cell 8ATR); *b* = pathlength.

ceutical industry. Moreover, in principle, FIA–FTIR spectrometry can provide a suitable tool for the analysis of active principles and drugs in pharmaceutical formulations, due to (i) its high concentration in this kind of products, and (ii) its absorption in the infrared region. However, at present only a few FIA–FTIR procedures have been described for this purpose. Table 3 presents – in a comparative way – the experimental conditions of some of these procedures.

In 1993, Garrigues et al. [21] developed a simple FIA–FTIR procedure for the determination of ibuprofene (2-[4-isobutylphenyl] propionic acid) in pharmaceuticals, using CCl_4 as solvent and carrier. In this solvent, the excipients are not soluble, and so, the drug can be directly determined at 1710 cm^{-1} (the carbonyl band) without any additional treatment. In a further study, the simultaneous determination of acetylsalicylic acid (AAS) and caffeine was described [22]. In this case, dichloromethane was used as solvent and carrier. The AAS and caffeine quantification were carried out at 1770 and 1661 cm^{-1}, respectively. Similar that in the method previously described for the determination of benzene in gasoline, a reverse flow system was proposed for a rapid quality control of this kind of pharmaceutical preparations.

Bouhsaim et al. proposed a FIA–FTIR procedure for the direct determination of paracetamol [23]. The method is based on the solubilization of paracetamol in a 10% (v/v) ethanol in CH_2Cl_2 solution, and direct absorbance measurement at 1515 cm^{-1}. The procedure can be carried out in both the "stopped flow" and FIA modes. On the other hand, Ramos et al. [85] developed a FIA–FTIR procedure, which includes on-line chemical derivatization, for the determination of acetaminophen in commercial formulations. The method is based on the alkaline hydrolysis of the analyte to produce *p*-aminophenol and its oxidation reaction with potassium ferricyanide to produce *p*-benzoquinone-monoimine, which eventually oxidizes to form b-benzoquinone. The reaction was carried out in aqueous media and at room temperature, using a micro-flow version of the circle cell. Measurements were carried out at the OH-phenolic deformation (1274 cm^{-1}), and the aromatic ring mode (1498 cm^{-1}).

In a further study, Bouhsaim et al. proposed the simultaneous determination of paracetamol, acetylsalicylic acid, and caffeine in pharmaceutical formulations. However, for this application a stopped flow mode and PLS data treat-

ment were used [86]. In other study, the simultaneous determination of propyphenazone (PFZ) and caffeine (CAF) in pharmaceuticals was described [87]. The method involves the dissolution of the active principles in $CHCl_3$, followed by filtration of sample solutions to remove the excipients. PFZ is then determined by absorbance measurement at 1595 cm^{-1}, and CAF by using the first derivative values at 1712 cm^{-1}. Additionally, the proposed system incorporates a distillation unit for the on-line recycling of the $CHCl_3$ (used as a carrier and solvent), which provides an environmentally friendly analytical methodology, and reduces cost and side-effects of the production of laboratory waste. In a further study, the same manifold was used for the determination of ketroprofene in pharmaceuticals [88]. The dissolution of the active principle was carried out in CCl_4, which also was used as a carrier. The quantification was carried out at the carbonyl bands (1712 and 1666 cm^{-1}). On the other hand, Thatishaiyakul et al. [89] proposed a FTIR procedure for the simultaneous determination of ibuprofen and paracetamol in two compositions of pharmaceutical tablets. Quantification was carried out by measuring the absorbance at 1684 and 1740 cm^{-1}, respectively, using the baseline established at 1740 cm^{-1} for measurement correction. However, this procedure was developed in a batch mode.

Gallignani et al. reported the determination of antimony in pharmaceuticals such as glucantime and pentostam by flow analysis–HG–FTIR. The method is based on the on-line mineralization/oxidation of the organic antimonials present in the sample and pre-reduction of Sb(V) to Sb(III) with $K_2S_2O_8$ and KI, respectively; prior to the stibine generation by reaction with $NaBH_4$. The 1893 cm^{-1} band of the stibine was used for the quantification of the antimony [64,65].

Caffeine has also been determined in samples such as soft drinks, coffee, and tea. For example, Daghbouche et al. [27] developed a fully automated procedure for FTIR determination of caffeine in soft drinks. Samples were previously degasified by filtration, and then directly injected into a flow manifold and passed through a 100 mg C_{18} SPE cartridge, conditioned with methanol and water. After the cartridge has been cleaned with water, the caffeine was eluted with $CHCl_3$ and stabilized with ethanol. The flow injection recording was obtained by measuring the absorbance at 1658 cm^{-1} with a baseline correction established at 1800 cm^{-1}. In the same way, Bouhsain et al. [28] proposed an automated procedure for the determination of caffeine in coffee. In this case, the method involves the on-line extraction of caffeine with $CHCl_3$. Samples weighted inside empty PTFE cartridges were humidified with NH_3. Then, the cartridges were installed in a flow system, in which samples were extracted in a close-flow system with $CHCl_3$. Finally, the extract were introduced in a FIA system via a microflow cell and absorbance measured as a function of time at 1659 cm^{-1} with a baseline established between 1900 and 830 cm^{-1}. Additionally procedures have been described for the determination of caffeine in roasted coffee and tea, but using a batch mode [90,91].

5.4. Pesticides

Pesticides are organic and organometallic compounds, which contain functional groups very active in the IR region. For this reason, FTIR spectroscopy offers a natural and attractive way for the determination of pesticides. Different FIA–FTIR procedures have been developed for the determination of some pesticide formulations. On the other hand, for the determination of pesticides in matrixes such as water and soil, incorporation of a pre-concentration step, and/or the use of the stopped flow mode has been incorporated in the experimental designs, in order to enhance the analytical sensibility. Table 4 summarizes the experimental conditions of some FTIR spectrometric methods that will be discussed in this section.

In 1993, a simple FIA–FTIR procedure was proposed for the determination of carbaryl in pesticide formulations [24]. The method is based in the dissolution of carbaryl in dichloromethane from solid powdered samples, and direct measurement at the carbonyl band (1747 cm^{-1}). Absorbance measurements can be carried out in the continuous flow, or by using the stopped-flow mode; however, the second approach gave best sensibility. In a further study, incorporation of an analyte enrichment step was proposed to improve the analytical sensitivity, and then the detection limit (see “Antecedents”) [16]. In the same way, and by using a similar system, the simultaneous determination of carbaryl, and its major metabolism, 1-naptol in waters was reported [92]. Detection limit of 0.2 mg l^{-1} for both analytes was obtained after preconcentration of 100 ml of the sample. Quantification was achieved at 1746 cm^{-1} (carbaryl, C=O) and 1726 cm^{-1} (1-naphtol, C–O). In the same way, Kargosta et al. [93] developed a new strategy for the simultaneous determination of the pesticide naptam (*N*-(1-naphtyl)phtalamic acid (NAP)), and its metabolites (1-naphtylamine (NNA) and *N*-(1-naphtyl)amide (NphDA)) in natural water by FTIR spectrometry. In this case, the method consists of preconcentration of samples using conventional C-18 solid-phase extraction discs, subsequent elution with methanol and dissolution of the residues in dymethyl sulfoxide after vaporization of the extract, absorbance measurements by FTIR in the spectral region between 1500 and 1800 cm^{-1}, and prediction of concentrations of the components recovered using the PLS calibration method. On the other hand, Armenda et al. described a FIA–FTIR spectrometric strategy for the determination of Buprofezin in pesticide formulations, using $CHCl_3$ as solvent [94]. In a further study, the simultaneous determination of Folpet and Metalaxyl in pesticide formulations was reported [95]. The method involves the extraction of both active principles by sonification of the sample with $CHCl_3$ and direct measurement at the 1798 and 1672 cm^{-1} bands (see Table 4).

Cassella et al. [96] described a FIA–FTIR procedure for the determination of dithiocarbamate pesticides (Ziram and Thiram) in solid samples such as commercial formulations of

Table 4
Experimental conditions of different flow analysis–IR methods developed for the determination of pesticide

Sample	Analyte	Measurement criterion[a]	Technique mode	Carrier-flow rate Injection volume	IR cell[b] *b* (mm)	Reference
Commercial formulation	Carbaryl	A*c: 1747 cm^{-1} BLc: 1850–1650 cm^{-1}	FIA–FTIR and stopped flow	CH_2Cl_2 0.81 ml min^{-1} 300 μl	TFC-(ZnSe) 1 mm	[24]
Waters	Carbaryl	A*c: 1747 cm^{-1} BLc: 1875 cm^{-1}	Flow analysis–FTIR Preconcentration with SPE. Elution with CH_2Cl_2	CH_2Cl_2 0.26 ml min^{-1} (elution)	SFC-(ZnSe) 0.5 mm	[16]
Spiked waters	Carbaryl	A*c: 1741 cm^{-1} BLc: 1845 cm^{-1}	Preconcentration: with SPE cartridge. Elution with CH_2Cl_2	CH_2Cl_2 0.26 ml min^{-1} (elution)	TFC-(ZnSe) 0.5 mm	[92]
	1-naphtol	1D: 1726 cm^{-1} band $(P–V)_v$: 1280–1272 cm^{-1}				
Commercial formulations and spiked soils[c]	Ziram	A^*: 1522 cm^{-1} (area in the range of 1600–1460 cm^{-1})	FIA–FTIR	$CHCl_3$ 0.41 ml min^{-1} 430 μl	TFC-(ZnSe) 0.20 mm	[96]
	Thiram	A^*: 1381 cm^{-1} (area in the range between 1400 and 1315 cm^{-1})				
Pesticide	Ziram	A^*: 1522 cm^{-1} (area in the range between 1600 and 1400 cm^{-1})	On-line-VPG–FTIR	Nitrogen 80 ml min^{-1} −50 mg *	IRGC*-(ZnSe) 39 mm	[62]
Pesticide	Buprofezin	A^*: 1401, 130, and 1364 cm^{-1} (area in the range between 1415 and 1349 cm^{-1}) BLc: 1417–1347 cm^{-1}.	FIA–FTIR	$CHCl_3$ 0.56 mg ml^{-1} 500 μl	TFC-(ZnSe and BaF_2) 0.11 mm	[94]
Pesticide formulation	Folpet	A*c: 1798 cm^{-1} BLc: 1810 cm^{-1}	FIA–FTIR	$CHCl_3$ 1.28 mg ml^{-1} 500 μl	TFC-(ZnSe and BaF_2) 0.10 mm	[95]
	Matalaxyl	A^*: 1672 cm^{-1} (area in the range between 1667 and 1677 cm^{-1}) BLc: 1692–1628 cm^{-1}				

[a] Measurement criterion: A^* = absorbance at the maximum absorption band; A*c = corrected absorbance; BLc = baseline correction; 1D: first order derivative spectrum at the analytical band; $(P–V)_v$: peak to valley measurement.
[b] IR cell: TFC = Transmission flow cell-(windows material); *b* = pathlength. IRGC*: infrared gas cell (home made)
[c] Soil samples spiked with known amounts of each pesticide, and incubated for 2 weeks.

the pesticides and soils. In this case, the slurry (solid sample in chloroform) is injected in the FIA system, where the filtration is performed on-line to separate the un-dissolved material. All the operations involved in the proposed system – extraction, filtration, and measurement – are integrated in the experimental set-up, in order to avoid excessive manipulation of samples and standards. In a further study, the determination of Ziram was carried out by means VPG–FTIR spectrometry [62]. In this case, the method is based on the evolution of CS_2, after decomposition of dithiocarbamate ($C_6H_{12}N_2S_4$) with diluted H_2SO_4 at 50 °C.

5.5. *The determination of alcohols — organic solvents, alcoholic beverages, cosmetics, and blood*

The direct determination of ethanol in alcoholic beverages by IR spectroscopy (NIR and MID), without sample pre-treatment, and the interfering effect of sugars, was studied extensively by Gallignani et al. [12,25,26,97]. The researchers proposed derivative FTIR spectrometric procedures – carried out in a stopped flow mode – for the direct analysis of ethanol in alcoholic beverages – from beers to spirits –, using the analytical band of ethanol at 1046 cm^{-1}, taking into

Table 5
Experimental conditions of different flow analysis–IR methods developed for the determination of alcohols

Sample	Analyte	Measurement criterion[a]	Technique Mode	Carrier-flow rate Injection volume	IR cell[b] b (mm)	Reference
Alcoholic beverages	Ethanol	1D: 1046 cm^{-1} $(P–W)_v$: 1052–1040 cm^{-1}	Flow analysis–FTIR stopped flow	Water Continuous	TFC-(ZnSe) 0.029 mm	[25] [26]
Beers	Ethanol	A*c: 1693 nm BLc: 1657–1720 nm	Flow analysis–NIR stopped flow	Water Continuous	SFC-(quartz) 10 mm	[97]
Liquors	Etanol	A^*: 2305 or 2636 nm	FIA–NIR	Chloroform 2 ml min^{-1} 100 μl	SFC-(quartz) 1 mm	[98]
Chloroform	Ethanol	$A^*c_{(1066\ cm^{-1})}/A^*c_{(931\ cm^{-1})}$ ratio BLc: 835 cm^{-1}	On-line-VPG–FTIR	N_2 — 410 ml min^{-1} 25 μl	IRGC*-(ZnSe) 3.2 m	[49]
Alcoholic beverages	Ethanol	A^*: 1050 cm^{-1} Integrated area 1150–950 cm^{-1}	On-line-VPG–FTIR	N_2 — 300 ml min^{-1} 1 μl	IRGC*-(ZnSe) 3.2 m	[52]
Blood	Ethanol	A^*: 1050 cm^{-1} Integrated area 1150–950 cm^{-1}	On-line-VPG–FTIR	N_2 — 400 ml min^{-1} 10 μl	IRGC*-(ZnSe) 3.2 m	[55]
Alcoholic beverages Eau du cologne	Ethanol (1) Methanol (2)	Integrated absorbance 950–820 cm^{-1} (1) 1025–950 cm^{-1} (1 + 2)	On-line-VPG–FTIR	N_2 — 300 ml min^{-1} 1 μl	IRGC*-(ZnSe) 3.2 m	[53]

[a] Measurement criterion: A^* = absorbance at the maximum absorption band; A*c = corrected absorbance; BLc = baseline correction; 1D: first order derivative spectrum at the analytical band; $(P–V)_v$: peak to valley measurement.
[b] IR cell: TFC = transmission flow cell-(windows material); SFC: standard flow cell; b = pathlength. FC = flow cell.

account the concentration of sugars in the sample [25,26]. In a further study, the researchers reported a very simple near infrared spectrophotometric procedure for the simultaneous determination of maltose and ethanol in beer samples –carried out in a stopped flow mode, too; based on the measurement of the ethanol absorbance maximum at 1693 nm corrected with a baseline established between 1657 and 1720 nm, and using a 4.5% (w/v) aqueous solution of maltose as a reference [97]. On the other hand, in order to avoid the interfering effect of sugars, Trippart et al. [98] proposed a simple procedure for the determination of ethanol in liquor by FIA-NIR spectrophotometry. A liquor sample is equilibrated off-line with dried chloroform to extract ethanol into the organic phase. The organic extract is injected into a carrier stream of dried chloroform, monitoring the ethanol absorbance at 2305 or 2636 nm. Pérez-Ponce et al. developed methods, based on the on-line-VPG–FTIR technique, for the determination of ethanol in alcoholic beverages [52] and whole blood [55]. In both cases the integrated absorbance between 1150 and 950 cm^{-1} was selected as a measurement criterion. For the analysis of whole blood, a glass-bead packed reactor was employed in order to retain the partially decomposed matrix and to avoid clogging up the small reactor. In the same way, the on-line-VPG–FTIR technique was used for the direct and simultaneous determination of methanol and ethanol in liquid samples like alcoholic beverages and *eau de cologne* [53]. In this case, the measurement of the area of the transient recording obtained for the wavenumber range between 1025 and 950 cm^{-1}, and 950 and 820 cm^{-1} allows the determination of ethanol and methanol in the same sample by using a simple proportional equations approach. The signal corresponding to the integration between 950 and 820 cm^{-1} is due to the ethanol alone, while the integrated absorbance between 950 and 820 cm^{-1} corresponds to the contribution of both alcohols. In a further study, the simultaneous determination of both alcohols was carried out using PLS-FTIR for the analysis of the generated gaseous phase [54]. Table 5 summarizes the experimental conditions of the described methods. On the other hand, for the automated detection of methanol vapour as airborne pollutant, Bangalore et al. [99] developed a signal processing technique to detect the presence of methanol vapour in an open path FTIR measurement. In this case, an automated detection algorithm was implemented through the direct application of digital and pattern recognition methods to short segments of FTIR interferograms. To test the data analysis methodology, a pollutant source of methanol vapour was simulated by the use of open air active bistatic, passive terrestrial, and passive laboratory spectrometer configurations. A low rate of false detection (lower than 0.5%) was achieved.

5.6. Sugars—the determination of sugars in diverse matrixes

Black et al. [100] published a paper entitled "*FTIR Spectroscopy as a powerful tool for the study of carbohydrates*

in aqueous solutions". In this work, FTIR spectral investigations were undertaken in aqueous media – in a batch mode – in order to facilitate the assignments of vibrational bands of sugars such as glucose and fructose, and to provide information about the anomeric form of sugars in aqueous solutions. Nowadays, the infrared spectrometry is one of the most used detection techniques – in both the NIR and the MID regions – for the determination of sugars in matrices as varied as juice fruits, soft drinks [40,43–46], alcoholic beverages [25,26,42,97], blood [35,101–103], etc.; and some of them have been developed in flow systems. The field is so broad that it can be the subject of a single paper, and a very extensive one. The reason of this success is due to the presence of high concentration of sugars – in general – in these matrices, and because they show a characteristic absorption spectrum in one of the transparent regions that the water presents in the infrared (see Fig. 5A). The methods of analysis that have been developed include from quality control methods, to detect the adulteration of food products to the HPLC–FTIR coupling, used in the separation and selective detection of sugars mixtures [47,48]. For this reason, the purpose of this work is not to make an exhaustive revision on the topic. Nevertheless, some papers will be discussed, papers which in our opinion summarize some of the most representative strategies that have been used in the determination of sugars.

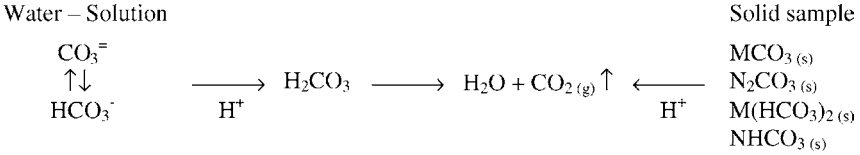
Kemsley et al. [104] proposed a rapid and quantitative method for the analysis of sugar mixtures (sucrose, glucose and fructose). In this work, it is investigated the suitability of the FTIR spectroscopy in the MID infrared, as an analytical technique for the analysis of sugar mixtures in industries such as soft drinks and brewing; and its potential for on-line monitoring. The proposed method is based in the K-matrix approach [105,106]. The method has been applied to the analysis of soft drinks and synthetic samples containing mixtures of glucose, fructose and sucrose. On the other hand, Lendl and Kellner, proposed in 1995 a new methodology for the determination of sucrose in complex aqueous matrices by FIA–FTIR. The method is based on the enzymatic hydrolytic cleavage of fructose by means of invertase to α-D glucose and β-D fructose (see "Antecedents") [29]. In a further study the researchers published a comparison between univariate and multivariate strategies for the determination of sucrose in fruit juice by FIA–FTIR [45].

Le Thanh and Lendl developed a fully automated method for the rapid determination of organic acids (citric, malic and tartaric acid) and sugars (glucose, fructose, and sucrose) in natural juice fruit samples and soft drinks by SIA–FTIR [41]. A convective interaction media disc (CIM) carrying quaternary amino moieties was added as a solid phase extraction column to the flow system. Upon injection of the sample, the organic acids were completely retained on the CIM disc, whereas sugars passed to the flow cell. The organic acids were subsequently eluted by injection of an alkaline (pH = 8.5) 1 M sodium chloride solution and recorded in their fully deprotonated from as a second flow injection peak. In both cases, the FTIR spectra (900–1500 cm^{-1}) corresponding to the peak maxima were selected for data evaluation. Two PLS models, one for sugars, and the other one for organic acids, were constructed based on the analysis of the analysis of standards containing all six analytes. On the other hand, Vonach, Lendl, and Kellner [47,48] proposed the use of FTIR spectroscopy as a molecular-specific detector for HPLC in an aqueous phase, focusing the chromatographic separation of sugars (sucrose, glucose, and fructose) in beverages. In this case, the separation was achieved with an isocratic HPLC setup using an ion exchange column. The FTIR detection of the C–O bands of the three sugars was performed in real time with a 25 μm flow cell without elimination of solvent.

The NIR infrared region was also used extensively for the determination of sugars in different matrices, generally using multiparametric calibrations [107–114].

5.7. Anions—the determination of anions such as carbonate and nitrite

Infrared spectrometry has been used for the determination of some anions such as carbonate, phosphate, and nitrite. The FIA–FTIR determination of phosphate is based on the pH modulation approach. The principle involves changing the sample solution from about pH 5 to pH 13 by injection of a concentrated base into the buffered sample stream, to convert the hydrogenphosphate anion ($H_2PO_4^-$) into the phosphate anion present at pH 13. The pH modulation approach is accompanied by strong spectral changes of the anion $H_2PO_4^-$, which shows strong absorption at 1159, 1078, and 941 cm^{-1}, to a single strong absorption of PO_4^{3-} at 1009 cm^{-1} [30,115]. Lendl et al. reported the determination of phosphate in soft drinks, by means the pH modulation approach, but using a quantum cascade laser as a MID–IR light source, in order to enhance the analytical sensitivity of the analytical system [30]. Pérez-Ponce et al. proposed a simple on-line-VPG–FTIR procedure for the determination of total carbonates (CO_3^{2-} and HCO_3^-) based in the on-line conversion of all the different carbonate chemical forms to $CO_{2(g)}$, through the on-line acidification of the sample [57–59]. The quantification of total carbonates was carried out using the 2350 cm^{-1} band of CO_2.



where M and N represents the cationic species in the salt, with oxidation state of (+2) and (+1), respectively.

Table 6
Experimental conditions of different on-line-VPG–FTIR methods developed for the determination of anions such as carbonate and nitrite

Sample	Analyte	Measurement criterion[a]	Technique mode	Carrier-flow rate injection volume	IR cell[b] b (mm)	Reference
Waters	Carbonate	A^*: 2350 cm^{-1} Integrated absorbance 2500–2150 cm^{-1}	On-line-VPG-FTIR	Water — 0.4 ml min^{-1} N_2 — 300 ml min^{-1} 100 μl	IRGC*-(ZnSe) 3.2 m	[57]
Waters	Carbonate	A^*: 2350 cm^{-1} Integrated absorbance 2500–2150 cm^{-1}	On-line-GPV-FTIR	Water — 0.6 ml min^{-1} N_2 — 200 ml min^{-1} 100 μl	IRGC*-(ZnSe) 3.2 m	[58]
Sediments	Carbonate	A^*: 2350 cm^{-1} Integrated absorbance 2500–2150 cm^{-1}	On-line-GPV-FTIR	N_2 — 50 ml min^{-1} 20 mg	IRGC**-(ZnSe) 39 mm	[59]
Apatites	Carbonate	A^*: 2350 cm^{-1} Integrated absorbance 2500–2150 cm^{-1}	On-line-GPV-FTIR	N_2 — 50 ml min^{-1} 50 mg	IRGC**-(ZnSe) 39 mm	[60]
Waters	Nitrite	A*c: 1876 cm^{-1} BLc: 1879–1872 cm^{-1}	On-line-GPV-FTIR	Water — 2.0 ml min^{-1} N_2 — 25 ml min^{-1} Continuous	sIRGC*-(ZnSe) 10 cm	[116]

[a] Measurement criterion: A^* = absorbance at the maximum absorption band; A*c = corrected absorbance; BLc = baseline correction.
[b] IR cell: infrared cell-(windows material); b = pathlength; IRGC*: multiple path IR gas cell; IRGC**; IR gas cell (home made); sIRGC: standard infrared gas cell.

For the determination of carbonate in waters, the manifold incorporates a heated gas permeation unit (GPU) [57], or a microwave oven [58], in order to encourage the removal of CO_2 [58]. On the other hand, for the analysis of solid samples [59,60], the strategy selected consists in the direct injection of acid into the reactor, containing the sample previously weighted (see Table 6).

For the analysis of nitrites, Gallignani et al. recently described an on-line-VPG–FTIR procedure based on the generation of nitric oxide ($NO_{(g)}$), by means of the on-line reduction of nitrite by the ascorbic acid action. The absorbance of NO is measured at 1876 cm^{-1}, using a background correction established between 1879 and 1872 cm^{-1} [116].

6. Current state of the flow analysis-IR techniques and new trends

Throughout this work several papers that have marked the origin, evolution and development of these interesting and powerful analytical technique have been presented. Furthermore, we attempted to provide a sample of the many possibilities that these techniques offer to confront the analysis of real and complex samples. On this account, different methodological approaches and applications which use different strategies and work philosophies to solve problems have been presented. Within such a frame, we can observe an enormous potential for the analysis of those samples in which the analytes are found in relatively high concentrations (gasoline, active principles in the commercial formulas of pharmaceutical products and pesticides, etc.). In a lot of cases, the flow analysis-IR techniques allow the direct analysis of one or more analytes, even in complex samples. In these cases, potential problems that may arise due to interference effects of the matrix – basically from the spectral type – have been solved by correcting the absorption of the analyte by using an appropriate base line, or by using derivative spectroscopy. In the same way, the incorporation of multiparametric software, such as the PLS, has resulted very successful and practical. Regarding the limited sensitiveness that IR spectrometry presents as a detection way in comparison to other spectroscopy alternatives (fluorescence, UV–vis molecular absorption, etc.), it is clear that this limit is originated mainly for the restriction in the pathlength, that is imposed by the solvents' transparency. In this sense, the incorporation of preconcentration stages by SPE and/or the use of solvents with higher transparency level (such CCl_4, $CHCl_3$, etc.) that allow the use of bigger pathlengths (several mm) can provide practical and simple solutions to the problems posed. In this general frame, in recent methodological developments, it is observed an important tendency to the miniaturization and automatization of the proposed designs, in which it is also pursuit to approach and include stages of the sample treatment such as the dissolution and filtration, etc. On the other hand, Lendl et al. [30] recently reported that compared with that a Fourier transform spectrometer, the signal to noise ratio could be improved at a factor of 50, by using of a quantum cascade laser (QCL) as a MID IR source. The QCL lased a several wavelengths closed to each other within a few wavenumbers, hence fitting well to the broad absorption bands of molecules in liquid phase. Additionally, by using this type of light source, optical path length more than 100 μm could be used even in aqueous matrixes, which reduces the danger of cell clogging, and increases the sensibility of the analytical system. Based on these results, the use of QCL appears as a very promising MID–IR light

source into the infrared spectrometric analysis, and it will be – for sure – the objective of new investigations in the future [30,117].

On the other hand, analyte conversion to a gas phase, done either by selective volatilization of the analyte – or the sample in its whole form – or by generation of a gas phase through a chemical reaction, represents a fascinating alternative within the infrared spectrometry. In these cases, the transparency of the blank, as well as the cells availability with pathlengths of several meters opens undoubtedly new horizons and perspectives to this instrumental technique. At this point it is important to emphasize that the gas phases' generation, by formation of a new product through chemical reactions involves the separation of the analyte from the matrix, and therefore the separation of a lot of interferences present in the sample. This fact provides a special appeal to the methodological proposals. Moreover, it is possible to think about incorporating pre-concentration systems to improve even more the sensitiveness of the studied systems. In this panorama, proposal of the usage of the FTIR as a sensible and selective detector for the determination of the elements that form hydrides opens an enormous window of applications, which undoubtedly will be consolidated in a not very distant future. Given all the beforehand exposed, it is clear that the on-line gas phase generation is undoubtedly one of the most attractive ways for the FTIR detection nowadays.

On the other hand, HPLC and CE are powerful and well established analytical techniques of separation, and hence they have been incorporated in different detection techniques, including FTIR spectrometry. In this sense, it is important to point out that the HPLC–FTIR and CE–FTIR coupling shows an important growing in the last years, providing solution for the analysis of complex and real samples. It is possible that in a near future, due to the amount of successful and relatively simple proposals that the infrared detection in flow analysis systems has offered, multiples analysis in real and complex samples are accomplished; an important growth in the number of researchers that will incorporate in their laboratories IR instrumentation will be observed.

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