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An Overview of Approaches in Liquid Chromatography Flame ionization Detection

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The history of LC/FID coupling from conveyor type interfaces to the most recent developments of nebulizer coupling systems is reflected

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Abstract

Several attempts to combine high performance liquid chromatography (HPLC) with flame ionization detection (FID) have been made since the 1960s. Elaborated systems were developed to overcome problems such as detector overload by use of organic solvents in HPLC or transfer of non-volatile analytes into FID. Almost twenty years after the first successful applications by solvent evaporation based techniques, subcritical water high temperature liquid chromatography opened the door for novel approaches to combine HPLC with FID. Direct coupling without pre-evaporation steps of signal disturbing organic solvents became possible and new instrumental developments resulted in capillary jet interface systems. These systems are suitable for a broad range of volatile and non-volatile analytes, which led to a significant increase of publications. This review discusses the most important developments of LC/FID coupling and summarizes its field of applications.

1. Introduction

Several HPLC based analytical methods with various detectors are available for a detailed characterisation as well as quantification of pharmaceutical impurities [1]. According to the ICH Q3A Guideline the pharmaceutical impurities are classified into (i) inorganic impurities, (ii) organic impurities and (iii) residual solvents. One of the most frequently used detectors for the analysis of organic impurities is the UV- or Diode array (DA) detector [1, 2]. However, UV- and DA-detection methods are only useful if the analytes have a suitable chromophore [3, 4]. Substances without chromophore are commonly detected by Refraction Index (RI) or Electron Light Scattering Detectors (ELSD). The ELSD is well applicable as LC detector in case of non-volatile compounds, and analysis of, e.g., lipids, sugars [5] and pharmaceuticals [6] highlighted its broad application range. However, a quantification by ELSDs is limited [2] because the ELSD is known to have a non-linear response [7]. RI in contrast to ELS detection, has a limited sensitivity, is temperature dependent and shows interferences as well as baseline drifts by application of solvent gradients [5]. All of these detection modes have their limitations in qualitative and quantitative analysis and, therefore, reviews on analysis of pharmaceuticals and their by-products revealed MS analysis as method of choice [8]. ~~In terms of quantification, MS such as all other mentioned LC detectors have the necessity of reference materials or closely matching internal standards (ISTD), which in particular is a problem for unknown impurities. After unequivocal identification, the required reference materials have to be synthesized by time consuming and high priced procedures.~~ All of these drawbacks demonstrate that there is a need for a robust and almost maintenance free detector to overcome the above-mentioned limitations of quantification during synthesis of pharmaceutical and chemical products. The FID with its carbon depending response rather support a fast semi-quantitative screening of pharmaceutical and chemical products in general, then determining the chemical structure as done by MS methods.

The flame ionization detector (FID) commonly applied in gas chromatography (GC), is known to be a robust and precise detector for the analysis of carbon containing materials. It provides a high concentration related linearity as well as linear response in the order of 10^4 to 10^7 , delivers a signal proportional to the

carbon content of the analyte, and allows the estimation of analyte concentration directly out of the obtained signal [9-11]. Use of reference materials, as required for other LC detectors, is not necessary for semi-quantitative impurity screening and investigation of volatile and non-volatile analytes by LC/FID. In contrast to LC/FID, GC/FID analysis of non-volatile analytes is only possible by time consuming sample preparation and pre-treatment such as derivatization.

In the following, we will discuss early LC/FID interfaces that used a chain, moving wire or disk for uptake of an organic mobile phase prior to detection to prevent FID signal saturation. In the early 1990's the introduction of subcritical aqueous LC methods paved the way for LC/FID interfaces in the coming decades [12]. Direct LC/FID hyphenation became possible. In contrast to organic solvents, water only causes an attenuation of the signal without being detected. Therefore, aqueous LC represents a valuable application field for LC/FID coupling for the analysis of e.g. alcohols [13-15], pharmaceuticals [16] or lipids [17]. The drop cell interface [18, 19], fused silica based capillary jet interfaces [13, 20, 21], stainless steel capillary jet interfaces [22] or the nebulizer/spray chamber [23, 24] have become promising techniques, capable to detect a wide variety of volatile and non-volatile compounds.

2. Early Developments

2.1 Conveyor Interfaces

The first types of LC/FID interfaces are known as conveyor type interfaces (Figure 1), named according to the mechanism of solvent uptake and evaporation processing by a moving wire or belt. The first LC/FID interface was issued by Haahti and Nikkari in 1963 [25]. Conveyor type interfaces had three major parts in common: first - a circulating (or feeding) chain, wire or belt; second - an air stripping chamber to evaporate the eluent with inert gases such as argon [26] or helium [27, 28]) used in later systems; and third – a pyrolyzation chamber, for pyrolysis of analytes attached onto the wire or belt. The pyrolysis products then were swept into the FID using helium or hydrogen as carrier gas.

The system by Haahti and Nikkaris suffered from loss of analytes and high electrical noise generated by the chain mesh [29]. Later on this problem was targeted by use of a platinum chain which vertically passed through the FID flame, by that the collector electrode was located concentric to the chain [30]. A more complex interface was published in 1964. The authors used a transport wire instead of a chain for solvent uptake. These early designs suffered of poor reliability and the transport mechanisms were susceptible to failures [31].

The concept was improved and in 1967 the Pye LCM Liquid Chromatograph became the first commercially available LC/FID interface [32]. To enhance the limit of detection, an oxidizing chamber was implemented. After evaporation of the solvent, the sample undergoes combustion to carbon dioxide and water. The carbon dioxide then is reduced in the presence of hydrogen and a nickel catalyst to methane [31, 32]. The pre- combustion/reduction enhanced the sensitivity by one order of magnitude.

Within the following decades, slight changes of the operation principles were made, e.g. a modified version of the Pye LC by improvement of the belt and eluent applicator [33]. Other authors transferred the eluent onto the belt using a spray mechanism [34] or exchanged the belt by a wire [27]. The modifications

enhanced the obtained detection limits by a factor of up to 50 in comparison with earlier systems [34].

Figure 1. Wire based conveyor type interface according to Privett and Erdahl (1978) [28]

Within the first decades, analysis by moving wire interfaces focused on non-volatile compounds such as squalene [25], synthetic rubber samples and polystyrene [33], albumin, glucose and cholesteryl [28] or diphenylhydrazine, phosphatidylethanolamine or sphingomyelin in environmental samples [35].

The first application of LC/FID interfaces for volatile compounds was reported by Karmen [36]. In contrast to former systems, the author used the nitrogen steam inside the drying tube as carrier gas to transport volatile analytes into the FID. A summary of the investigated compounds and the corresponding references is given in Table 1.

One of the last publications of wire based LC/FID systems was published in 1986 using the Pye LCM 2, a development of the Pye LCM system [27]. The Pye instruments were produced between 1968 and 1974, after that Young et al. patented a nebulizer spray chamber based system, however the Pye systems are known to be the only commercially available LC/FID systems.

2.2 Rotating Disk Interfaces

Cobler et al. (1968) patented a second type of conveyor interface: the rotating disk [37]. In the setup a rotating perforated metal disc carried the eluent from a gel permeation column into the FID flame. Except for the difference between disk and belt (or wire) the major three compartments of solvent application, evaporation and pyrolysis stayed the same (Figure 2). In contrast to wire based systems, the disk relied on

low flow rates and required cleaning before further uptake of eluent. The authors successfully applied the system to the detection of e.g. polystyrenes [29].

Figure 2. Disk based conveyor type interfaces according to Cobler et al. (1968) [37]

Further disc type interfaces used a ceramic disc, heated by an infrared lamp to evaporate solvent and a two part detector in which the flame was located below the disc and the electrodes were placed above [38] or a vertically spinning porous alumina disc other systems used a ceramic coated ring instead of a disc [39]. A more sophisticated type of disk interface was presented in 1989 [29]. The transport mechanism was made of a two-part disc mounted on the shaft of a stepper motor fixed to the main chassis of the instrument. 40 quartz rods were connected to the disc, as shown in Figure 3b. The eluent was deposited at the delivery point onto the fused silica rods. The disc mechanism was positioned at a slight angle from the horizontal, so that the liquid tends to flow towards the end of the rod. Once liquid was deposited onto a rod, the rod moved over the evaporation air flow. The volatile eluent was completely evaporated and the rod was stepped into the center of the flame, where any carbon containing residue was combusted. After cooling down, the rod then reaches the liquid uptake stage again [29].

The system linearity was examined using pyrene, whereby the detector was observed to be overloaded at 20 μg applied. In further experiments the authors used a homologues series of alkanes (C12 to C40). The response was found to reach a plateau at C22 to C40, indicating a non-linear response behavior [29].

Figure 3. Quartz rod assembly by Malcome-Lawes and Moss (1989) [29] (a) Complete detector unit; (b) Quartz rod solvent transport system.

Table 1. Type of LC/FID systems with corresponding literature and exemplary investigated compounds and sample type

Analytes	LOD	Sample Type	Reference
Conveyor type interfaces (Wire or Belt)			
Squalene, cholesteryl palmitate, oleyl alcohol	n/a	Human sebum, human serum	[25]
Polystyrene	n/a	Synthetic rubber	[33]
Squalene	n/a	Squalene mixture	[26]
C12 to C40 alkanes, pyrene	n/a	Alkane mixture	[29]
Methyl esters	n/a	Soybean oil glycerolysis mixture	[17]
Triolein and phospholipids	n/a	Blood serum, liver and kidney tissue	[35]
Cholesteryl oleate and triolein	n/a	Cholesteryl oleate and triolein mixture	[28]
Fatty acid methyl esters, sterole esters and tri glycerides	n/a	Fatty acid methyl esters, sterole esters and tri glycerides mixtures	[36]
Xylose, glucose, sucrose, maltose and lactose	110 to 400 ng	Sugar standard mixture	[27]

Conveyor type interfaces (Disk)

Gel permeation chromatography	n/a	Standard mixtures	[37]
No application mentioned	n/a	Parathion, methyl parathion and diazinon mixture	[40]
No application mentioned	n/a	-	[38]
n-eicosane	2ng/sec	Tetradecane mixture	[39]
Hanging drop interface			
Volatile organic compounds	0.5 to 9 ppm	Standard mixtures	[18]
Phenols, aliphatic alcohols, methylene chloride, bromochloromethane, 1,2-dichloroethane, chloroform	240 ng ¹	Standard mixtures	[19]
Capillary jet interface			
Parabens and phenols	10 ng ethanol, 25 ng phenol, 36 ng acetic acid	Standard mixtures	[14]
Alcohols (C ₁ – C ₅)	0.1 to 1 ng ²	Standard mixture	[21]
Alcohols (C ₄ - isomers)	3 to 10 ng	Standard mixture	[41]
Alcohols and aldehydes	0.2mg/mL 3 to 10ng	Standard mixture	[20]
Alcohols	1 ng	Standard mixtures	[22]
Alcohols (C ₁ – C ₄)	26 to 57ng	Wine	[42]
Alcohol in beverages	n/a	Alcoholic beverages	[13]
Carbohydrates, amino acids, organic acids and bases	n/a	Standard mixtures	[43]
Nebulizer/Spray chamber interface			
i.e. alcohols, glycols	0.23 ³ to 10.23 ⁴ μg	Standard mixtures	[23, 24]

¹Lowest concentration measured; ²Expected LOD according to [41]; ³Benzyl alcohol; ⁴Aniline, n/a authors mentioned no detection limits

2.3 Solvent limitations

The solvent became the limiting factor of former LC/FID couplings. Organic solvents still had been the only choice in reversed phase HPLC analysis until the first publication of subcritical water liquid chromatography by Smith and Co-workers [44]. Smith et al. addressed the observations of Hawthorne et al. [45], who exploited the ability of water to extract non-polar compounds at elevated temperatures. In experiments, Hawthorne et al. showed that the dielectric constant of water is lowered by a simple raise in

temperature (Figure 4a). The authors subsequently extracted polar, moderately polar, and non-polar organics from environmental solids by sequentially increasing the extraction temperature from 50°C (for polar organics, e.g., chlorophenols) to 400°C (for very nonpolar organics, e.g., >C-20 alkanes) [45]. Smith used the results and created a method for separation of parabens, phenols, barbitones by only water LC [46].

Figure 4. Physicochemical properties of Water, Methanol/Water and Acetonitrile/Water mixtures between 0 and 250°C [47]. (a) dielectric constant, (b) surface tension and (c) viscosity.

The fundamental work of Hawthorne and Smith resulted in the investigation of analytes suitable for high temperature only water LC. In 1999, Yang et al. [12] conducted separation of BTEX by conventional C18 RP columns. Chienthavorn and Smith published the successful separation of sulfonamides in 1999 using buffered water as eluent [48]. Recent publications show the potential of high temperature liquid chromatography and the range of possible analytes that can be investigated by the technique [49].

2.4 Capillary Column Interfaces

Based on water as solvent, a novel interface type evolved: the capillary jet interface. The fundamentals of capillary jet interfaces originate from coupling experiments of supercritical fluid chromatography (SFC) to FID. A modified FID jet was used to improve the flame stability and increase of the sensitivity of detection [50]. The first direct capillary-based interfacing of HPLC and FID was presented by Miller and Hawthorne [22] and Hooijschuur et al. [41] (Figure 5a and b).

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Figure 5. Scheme of capillary based interfaces: (a) Setup of the LC/FID jet interface by Miller and Hawthorne (1997) [22], (b) Up-side-down LC/FID interface by Hooijschuur et al. (2000) [41] (c) Jet interface by Yarita et al. (2002) [13].

Miller and Hawthorne [22] used a small internal diameter stainless steel restriction capillary to prevent mobile phase flash evaporation. The effect occurs by entrance of the liquid into the heated capillary and causes spontaneous expansion of the former liquid into the gaseous phase. In addition, the capillary serves as an evaporation jet to introduce the analyte directly into the flame. The authors adjusted the capillary 3 cm beneath the FID jet (Figure 5a) and created a thermo-spray of 300 to 400°C [22]. Hooijschuur et al. developed a μ LC/FID system and placed an inductive pre-heated stainless steel capillary upside down (Figure 5b) into the FID to improve the transport of the generated aerosol by means of gravitation [41]. Guillaume et al. [21] used a fused silica tubing, preheated by a GC oven to directly link the LC to the FID. A comparable interface was built by Yarita et al. [13] and Nakajima et al. [42] where the authors used an external heating device (Figure 5c).

In contrast to conveyor type interfaces, the analytical focus was extended from non-volatile to volatile compounds, too. The first capillary jet interfaces focused on parameter optimization and investigation of ethanol in beverages [22], alcohols and aldehydes [20]. Later ones successfully separated and quantified samples containing, e.g., methanol, ethanol and aldehydes using a 0.5mm ID PRP-1 HPLC with a flow of $50 \mu\text{L min}^{-1}$ [20]. The method was adapted by Yarita et al. [13] and Nakajima et al. [42] for analysis of ethanol in beverages, whereby the stainless steel capillary was replaced by a fused silica capillary that additionally functioned as a passive split for the LC eluent. Yang et al. used conventional 2 or 4 mm I.D.

columns [43] and split of a column flow of 1.24 mL min^{-1} down to $48 \text{ }\mu\text{L min}^{-1}$ to support complete evaporation of the eluent. The interface was capable to introduce amino acids, carboxylic acids and carbohydrates for quantification into the FID. A post-column split was also used by Fu et al. for separation of alcohols, phenols and carboxylic acid on a Polymer RP-1 (PS-DVB) column with 4.6 mm I.D and 150 mm length [14].

2.5 Drop Headspace Interface

The hanging drop interface was developed beside capillary based LC/FID interfaces [18, 19] and functions by drops formed at the tip of a fused silica tubing that fall unobstructed into a waste reservoir. A linear flow of helium passes the growing drop and enhances analyte evaporation. The analyte enriched helium stream flows through a deactivated fused silica transfer tubing into the FID (Figure 6a). In contrast to Bruckner et al. who investigated 1-butanol, 1,1,2-trichloroethane, butanone, chlorobenzene, toluene, ethylbenzene and o-xylene, Quigley et al. used the interface for the analysis of e.g. resorcinol, benzyl alcohol, phenol, phenyl-ethyl alcohol, o-cresol and p-cresol [19].

Figure 6. (a) Scheme of the hanging drop device developed by Bruckner in 1997 [18] (WRP-LC column: water only reverse phase column). (b) nebulizer/spray chamber assembly by Young et al. (2012): (1) carrier flow, (2) nebulizing gas, (3) nebulizer, (4) spray chamber, (5) condensate to drain, (6) connection to detector base. [23].

2.6 Concentric micro flow nebulizer

The micro flow nebulizer interface by Young et al. presents the latest development in LC/FID hyphenation [23, 24]. The set up contains a modified micro-concentric nebulizer adapted to a centrifugal spray chamber with a dimple. The column effluent is nebulized by use of a nebulizer gas at ambient temperatures. Samples are not directly introduced into the FID, in contrast, the sample aerosol is transferred via a carrier gas through a glass tube into a modified FID (Figure 6b) [23]. To avoid flash evaporation, a restrictive capillary is used to keep a sufficient backpressure in the system and in addition to work as capillary jet of the micro flow nebulizer. Alcohols, aliphatic and aromatic ketones, acids, amines and glycols were successfully separated by RP-C18 columns and measured by the micro flow nebulizer spray chamber interface. The broad spectra of investigated volatile and semi-volatile analytes are presented in two major publications [23, 24].

3. Advantages and limitations of LC/FID interfaces

Table 2 summarizes the main advantages and disadvantages of the different interfaces.

Table 2. Advantages and Disadvantages of the different types of LC/FID interfaces

Type of Interface	Advantages	Disadvantages
Conveyor	<ul style="list-style-type: none"> - Analysis of non-volatile analytes - Organic solvent mobile phase - Linear response - Low LOD for non-volatiles 	<ul style="list-style-type: none"> - Bulky Setup - Susceptible to failures - Additional drying gas required - Additional gas for analyte transfer required
Drop Headspace Cell	<ul style="list-style-type: none"> - Analysis of volatile analytes - Linear response - Low LOD for volatiles 	<ul style="list-style-type: none"> - Only water mobile phase - Analytes require high air/water partitioning coefficient - Additional gas for analyte transfer required
FS Capillary Jet	<ul style="list-style-type: none"> - Analysis of non-volatile analytes - Analysis of volatile analytes - Linear response - Low LOD for volatiles - No additional nebulizer gas required 	<ul style="list-style-type: none"> - Only water mobile phase - Silica induced clogging
SS Capillary Jet	<ul style="list-style-type: none"> - Analysis of non-volatile analytes - Analysis of volatile analytes - Linear response - Low LOD for non-volatiles - Low LOD for volatiles - No additional nebulizer gas required 	<ul style="list-style-type: none"> - Only water mobile phase
Nebulizer Spray Chamber	<ul style="list-style-type: none"> - Analysis of non-volatile analytes - Analysis of volatile analytes - Linear response for volatile analytes 	<ul style="list-style-type: none"> - Only water mobile phase - Non-linear response for non-volatile compounds - Matrix effects - Additional nebulizer gas required

A substantial advantage of the conveyor type interfaces is the ability to be used for high molecular non-volatile analytes such as bio-polymers. The analyte can be introduced as solid compound into the FID by the belt, disk or wire. In contrast, analysis by nebulizer based interfaces depend on the ability to transfer the analyte molecules into the gaseous state or by the generated solvent spray into the FID. The fast evaporation of the solvent can cause crystallization of the analyte at the tip of the nebulizer capillary.

However, most capillary jet interfaces are heated up to 400 °C, which supports the evaporation of the analyte. The spray chamber type interface works at ambient temperature, therefore only compounds which can be transferred by the solvent spray can be introduced into the FID as shown by the non-linear response of e.g. carboxylic acids. The order of applicability for non-volatile analytes is conveyor > capillary jet > nebulizer spray chamber > hanging drop.

The lowest LODs for volatile analytes are obtained by capillary based interfaces. Likewise for non-volatile analytes, the thermospray of capillary jet interfaces supports the evaporation of volatile analytes. Therefore, these types of interfaces show substantially lower LODs of e.g. alcohols (0.1 – 1 ng), followed by the hanging drop interface (240 ng) or nebulizer spray chamber (230 ng). Conveyor type interfaces cannot be used for volatiles' analysis.

The conducted studies on LC/FID systems showed that a linear response is obtained by each of the different types of LC/FID interfaces. Only the nebulizer spray chamber was found to have a non-linear response for, e.g., ethylene glycol at high concentration levels. According to the authors, it appeared that volatility was a major factor and discrimination in the spray chamber can be a reasonable factor for lower relative responses of compounds that were solid. Due to that, analytes which volatilize during the nebulization process are carried into the flame as a vapor, whereas less volatile analytes which would be transmitted in the droplets of the spray were lost to a more significant extent during transfer and detection [24].

Concerning the applicability of interfaces, the bulky disk and wire based conveyor type interfaces were known to be separate instruments which required a high amount of drying and carrier gas. Furthermore, the conveyor and pre-evaporation units were susceptible to failures. In contrast, most capillary based interfaces as well as the nebulizer spray chamber are designed to be easily installed into existing FID systems.

An undesired side effect of fused silica based jet interfaces is the occurrence of blockage as result of silica deposition. The silica is washed out of the glassware, column and fused silica capillary and by evaporation

of the solvent, the silica particles remain inside and at the tip of the capillary and form crystalline deposits (Figure 7). These crystals can cause two substantial problems: first – complete blockage of the capillary and second – crystal break-off. The crystal break-off can hit the detector electrode and result in undesirable spiking. A possible solution to partially overcome the problem was done by Miller and Hawthorne by use of stainless steel capillaries with larger IDs [22].

Figure 7. Silica formation at a fused silica capillary tip after 72 hours a) End of a new fused silica capillary, b) end of the fused silica capillary after 72 hours nebulization, with a water flow of $50 \mu\text{L min}^{-1}$

4. Conclusions and Perspectives

Coupling of LC/FID could become a complement to established LC detection methods such as light scattering detectors, UV detectors and mass spectrometers. Based on the required solvents for chromatographic separation, possible LC/FID target compounds have changed over time. The change of the FID sensitive organic solvents (e.g. methanol, acetonitrile) to aqueous LC resulted in the design of advanced direct interfaces. Analysts are no longer restricted to high boiling non-volatile compounds, capable to pass through the evaporation chamber of conveyor LC/FID interfaces.

Hyphenation of LC/FID by capillary jet interfaces resulted in novel applications. The broad range of UV insensitive analytes such as alcohols and aliphatic hydrocarbons can be quantified by LC/FID nowadays.

The use of pre-heated capillaries to support the evaporation of the mobile phase and introduction of analytes into the FID led to limits of detection close to those known from modern GC/FID systems. Fast

semi-quantitative analysis of solvents in pharmaceutical products without use of MS systems is possible by using LC/FID systems.

Nevertheless, LC/FID coupling holds the potential to be improved within the next decades. Novelties need to address the different FID systems of GC instrument manufacturer and should be designed to be easily installed to existing GC systems. Even more, the development of small interface-detector units should be addressed in future. A universal, cost effective and simple add-on detector for LC systems is not available until now.

Furthermore most systems are affected by clogging of transfer capillaries, as known from LC/MS probes. The exchange of these capillaries is difficult and requires experience. Novel systems might use robust, exchangeable capillaries ready to install such as known from LC/MS.

A substantial advantage of the FID in contrast to other detectors, is the semi-quantitative analysis of carbon containing materials. However, to date only response studies and prediction models for GC/FID analysis are available. From the beginning of LC/FID until now, comparison of GC/FID and LC/FID response data was hardly studied. Research should therefore focus on the response mechanism in LC/FID to provide a reliable data base for semi-quantitative response prediction as known in GC/FID.

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Highlights

The history of LC/FID coupling from conveyor type interfaces to the most recent developments of nebulizer coupling systems is reflected

The review discusses the most important developments of LC/FID coupling and summarizes its field of applications.

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