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Review

Review on recent applications of the liquid waveguide capillary cell in flow based analysis techniques to enhance the sensitivity of spectroscopic detection methods

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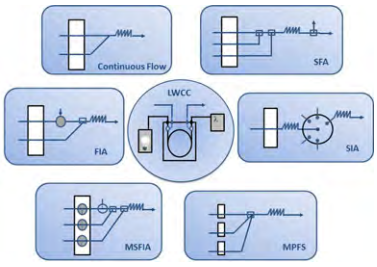
HIGHLIGHTS

- Advances in application of liquid core waveguide capillary cell are summarised and critically discussed.
- Different flow strategies using the LWCC are presented.
- Practical advantages and limitations in application are pointed out.

GRAPHICAL ABSTRACT



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ABSTRACT

Incorporation of long path length liquid waveguide capillary cell (LWCC or LCW) into spectrometric detection systems can increase the sensitivity of these by orders of magnitude (up to 500 times), and consequently can reduce the detection limits. The combination of the long path length spectrophotometry with flow methodologies can provide analytical solutions for various challenges in the field of environmental, biochemical and food chemistry.

In this present work, the analytical applications of the long capillary cells are summarised and critically discussed. A historical overview of the cell development is given; applications in different areas are presented and grouped by analyte type. Major improvements achieved based on the use of the LWCC in the analytical characteristics (like sensitivity and detection limit) are emphasised while some of the limitations are also discussed.

Contents

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1. Introduction

Molecular absorption spectrophotometry is one of the most used analytical detection technique in different application fields because it is accessible, robust, accurate, and versatile and fundamentally, a low cost technique [1].

Spectrophotometry is also the most common detection technique in flow analysis systems [2,3]. However, the limits of detection achieved with spectrophotometric methods might not reach the levels necessary for some analytical applications. In this scenario, different strategies can be applied to spectrophotometric flow analysis with the purpose to improve the sensitivity and the detection limit. As derived from the Lambert–Beer law, the absorbance value detected for a given concentration of the analyte is dependent upon the molecular absorptivity value of the compound and on the pathlength of the sample cell. Therefore, one way to increase sensitivity is to apply chemical derivatisation to form reaction products with increased molecular absorptivity. These applications often resort to newly synthetised reagents, and automation of these analytical procedures brings advantages in terms of reagent consumption and waste production. Other alternatives have been reported such as, pre-concentration/separation of the analyte by solid-liquid extraction or liquid–liquid extraction [4,5]. The preconcentration in the form of solid phase extraction is one of the most advantageous way since separation of the analyte from the matrix also enhances the selectivity of the method, although mainly organic solvents are needed for elution and the produced effluents can be hazardous [6,7]. Sample throughput is markedly decreased if the physical support (the solid phase) is to be reused, as total elution of the analyte and reconditioning of the column is needed. Automated SPE manifolds [8,9] consequently, are designed to use different separation ports simultaneously, and this way improve the sample throughput and repeatability.

The increase in the optical path length is an attractive alternative approach to improve the sensitivity in spectrophotmetric methods [10]. However, in classical spectrophotometric glass cuvettes for solutions, the increase of the optical path is physically limited by the spectrophotometer itself and by the assay volume available. In flow through configurations the limitations are emphasised by the increased dispersion of the reaction zone and by the increased attenuation of the incident light provoked by the light absorption on the walls of the flow cell. These difficulties limited the use of glass or quartz cuvettes to a maximum length of 10 cm. The development of multi-reflective (MRC) or liquid waveguide capillary cells (LWCC) has brought new possibilities in this area.

1.1. Multireflective cells

Multireflective cells make use of mirror-coated helical [11] or straight [12] capillaries inside which multi-reflective or multi-path behaviour can be observed. Ellis et al. [10] developed a multi-reflective flow cell with a relatively short length (<10 cm) glass capillary-coated externally with a reflective surface (silver or aluminium). By etching two windows into the coating surface, the introduction and collection of light at an angle of ca. 60° to the flow axis (Fig. 1a) is allowed. The light beam entering the capillary undergoes multiple reflections on the mirrored sidewalls until the exit slit is reached. Because of its longer effective optical path-length and lower dispersion, this cell was found to have markedly improved sensitivity when compared with a Z-cell [10]. It also showed much less susceptibility to the effect of refractive index variations than the alternative Z cell. In addition, the connections between the cell and the flow system are longitudinal to the flow axis, the accidental gas bubbles entering the flow cell pass through, without being trapped in the light-pass.

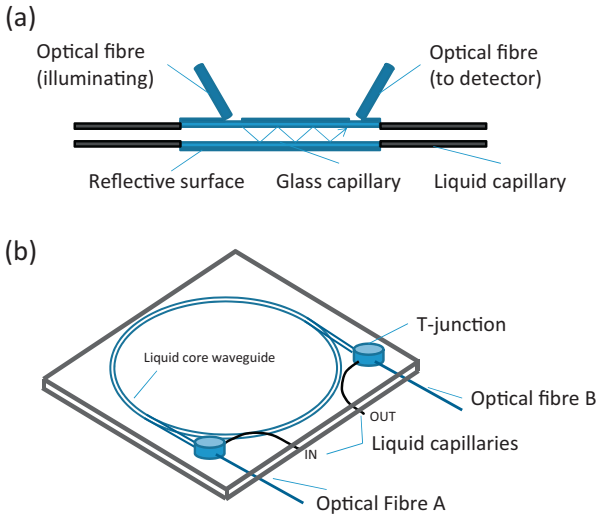


Fig. 1. Schematic presentation of the (a) Multireflective cell, (b) liquid waveguide capillary cell with axial illumination, adapted from WPI instrument handbook [91].

However, the multi-reflective cell's exterior mirror coating absorbs shorter wavelengths, and that can limit the application of these cells for measurements in the UV range [13]. Nonetheless, it was effectively applied in the development of FIA and SIA manifolds for the determination of molybdate reactive phosphate in natural waters of different origins [12,14,15], and of nitrate in estuarine waters [16].

1.2. Liquid waveguide capillary cell

The liquid core total internal reflection waveguide is a commercial alternative for measurements in liquid medium and devices with optical path of up to 5 m with capillary dimensions (ca. 250 $\mu L\,m^{-1}$) are available (Fig. 1b.). Such liquid waveguide capillary cells (LWCCs) provide low dispersion of the reaction zone and the developed methods with long optical path may attain exceptional analytical characteristics. Nanomolar determinations become easy to reach in a very simple, low cost and versatile way, as it can be concluded from the various reference works on the subject. Dallas and Dasgupta reviewed in 2004 [17] the initial technical and fundamental development of the cell, and its different configurations. In a 2007 review, Gimbert and Worsfold [18] gave a detailed description of the LWCCs summarising the environmental applications. Sun et al. [19] recently summarised the progresses in the application of Teflon AF (amorphous fluoropolymer) material in the fabrication of LWCC/LCWs, however this last paper was published at a local language and the information contained within might be difficult to retrieve. This present review aims on the succession of the two reviews published in 2004 [17] and in 2007 [18], and so recent analytical applications of the long capillary cells are summarised and are critically discussed. A historical overview of the cell development is given; applications in different areas published since the review in 2007 [18] are presented and listed by the analyte type. For earlier applications the reader is kindly asked to refer to these former publications. Major improvements in the analytical characteristics are emphasised, based on the use of the long capillary cell.

2. Total internal reflection phenomenon

The direction of a light ray is bent away from the normal interface when traveling from an optically denser to a less dense medium. The limit on this refraction angle is 90°. The angle of incidence where the angle of refraction becomes 90° is the critical angle (θ_c) [20].

Therefore, in order to total internal reflection occur, the ray of light must travel from a material with a higher RI to one of a lower RI and it must hit the medium interface at an angle greater than the critical angle. The critical and incident angles are measured according to the normal of the interface (in the present case perpendicular to the surface of the capillary), and the critical angle is specific to the material used. For the Teflon AF 1600 grade this angle is 9.9° and for Teflon AF 2400 it is 14.1°. These values are calculated based on the Snell's law and water as a core liquid:

$$\theta_c = \cos^{-1}\left(\frac{n_1}{n_2}\right)$$

where n_1 is the RI of the cladding material and n_2 is the RI of fluid core.

3. Characteristics of LWCCs

The first LCWs were used in the 70s with Raman spectroscopy and the capillaries were made of borosilicate or fused silica with a refractive index (RI) of 1.51 or 1.45, respectively. Therefore, it was only suitable for samples with RI higher than the material employed, such as organic solvents. For aqueous samples, the capillaries were needed to be fabricated from materials with much lower RI. The efficient solution appeared with the development of the new polymer Teflon AF. Teflon AF refers to a family of amorphous fluoropolymers of tetrafluoroethylene (TFE) and 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole (PDD) and has a refractive index (1.29–1.31) lower than that of the water (1.33) [21–23]. This new polymer is patented by DuPont and is commercially available since late 1980 in two grades: Teflon AF 1600 and Teflon AF 2400; the difference between them is based on the relative amount of the dioxole monomer in the basic polymer chain. This difference has effect on the optical properties of the polymers, RI of 1.29 and 1.31 for Teflon AF 2400 and AF 1600, respectively [22,24,25].

In 1998, Dress et al. [26] demonstrated that 5 μm layer thickness of Teflon AF 2400 was enough to confine the optical intensity to the liquid core avoiding any influence of the external environment and any absorption or scattering by the capillary material. A comparison between Teflon AF 2400 and other tested capillary materials confirmed that there is no light absorption in Teflon AF 2400 in opposition with the uncoated or silver coated glass tubes. With these low RIs, the construction of LWCCs using water as the optical core was enabled and broadened the field of applications. The high light transparency of Teflon AF also permitted working in a wide range of wavelengths (200–2000 nm) [27].

Teflon AF, with its porous structure, is permeable to gases and the adsorption of some species in aqueous samples can occur in its surface [28,29]. Air bubbles can adhere to it and cause signal distortion/baseline shifts [29]. Meanwhile, the porous structure can be exploited as a positive feature in the determination of gaseous analytes [28,30,31].

Teflon AF is chemically inert and is quite difficult to functionalize, as it is only soluble in highly fluorinated solvents [22–24]. These solvents promote the adhesion of Teflon AF with glass constituting the basis of construction of composite type configurations.

The LWCCs can be classified in two types regarding their construction, type I and type II [18]. Type I consist of solid Teflon AF tubing with low refractive index [32], as referred above. The light travels down the capillary and is totally internally reflected at the Teflon AF interface with the condition that the incident angle exceeds the critical angle; the light passing from an optically denser medium (that is water) to the interface with the less dense medium (that is Teflon AF) [33]. The type II cell consists of a fused silica capillary tubing (n_1 = 1.46) with an outer coating of Teflon AF with the

low refractive index [5,32]. The light travels down the capillary and is totally internally reflected at the interface between the outer fused silica capillary surface and the Teflon AF coating with the same condition referred above; the incident angle has to exceed the critical angle [25,33]. D'Sá and Steward [34] demonstrated that in the absence of imperfections in the quartz capillary or of scattering particles in the solutions, light cannot be trapped in the waveguide quartz wall, as there will always be a total internal reflection at the quartz/Teflon interface. The reflected light will than return to the quartz/water interface and will re-enter the core medium again.

The use of a thin layer of fused silica in type II cell protects the Teflon AF from the abovementioned undesirable effects since fused silica is impermeable to gases and avoids the direct contact between the sample and Teflon AF [21]. Moreover, the fused silica tubing acts like a backbone, providing physical stability while the external coating protects its surface from mechanical crack formation. Due to the hydrophilic inner surface the bubble retention is also reduced [21,25], is less vulnerable to light scattering and schlieren effects [35], it is easier to clean [29] than the type I alternative, and consequently has an improved signal stability.

The effective optical path length of type I cells is statistically indistinguishable from the physical path length. In type II cells, the theoretical basis to calculate the effective path length has not been established yet and it is determined experimentally. It was confirmed [21] to be slightly shorter than the physical path length (0.94 ± 0.01 times of its physical path length) because of the presence of the additional fused silica layer. It was shown to be dependent on the wall thickness and inner diameter of the LWCC, as light is not absorbed by the analyte while travelling in the cell wall. It also means that the difference in the effective path length should be more affected in the deep UV wavelengths of the spectrum [36] where the silica glass itself can absorb radiation.

3.1. LWCCs based on different materials

Besides Teflon AF, other materials can be incorporated in the liquid core waveguide cells if the total internal reflection conditions are fulfilled.

Keller et al. [37] evaluated fused silica capillaries surrounded by the doped silica cladding and a polyimide coating for absorbance measurements in methanol and in dimethylsulfoxide ($n_2 = 1.479$) based solutions. This material ($n_1 = 1.441$) under the experimental conditions studied, has a light (UV, visible and near infra-red range) guidance along the entire length of up to 50 m. This material was also evaluated for fluorescence measures and the results showed linearity up to 20 m length [38].

Later on, Korampally et al. [39] presented a new polymer constituted by organosilicate nano particles with a low RI of 1.16. The results obtained show a superior light guidance performance over Teflon AF although the integration of this material to waveguide coatings is not straightforward.

Nanoporous materials [40] are formed by introducing nanosized voids into a monolithic matrix material. The refractive index of this composite material is than, can be calculated as a weighted average of the refractive index of air ($n = 1$) and that of the host material. Therefore, the degree of porosity controls the optical properties of these materials. These materials offer considerable flexibility in terms of obtaining tuneable refractive indexes for the cladding. Additionally, surface modification [38] of these materials could be performed to contain active functional groups useful for attaching various biological probes.

Sugiya et al. [41] developed water-ice based flow cell as another option to Teflon AF 2400 in LWCCs. The ice chip wall has a RI of 1.309, but water soluble organic solvents cannot be used as a core media because of the solubilisation of the water-ice wall.

4. Working modes of the LWCCs

LWCCs can be connected through optical fibres to a light source and a detector, and the illumination in LWCC may be performed in axial and transverse mode[17].

In the axial mode, light is transported in and out of LWCC by optical fibres. This mode is commonly used for absorbance measurements [18]. In transverse mode the LWCC is illuminated through the sidewall and at the end of LWCC the light is transported to the detector by optical fibres. This mode is used for fluorescence measurements [17].

The commercially available LWCC employing Teflon AF from World Precision Instruments (WPI) with different path lengths from 50 to 500 cm with respective internal volumes of 125 up to 1250 μL, is applicable to absorbance measurements only, as only the axial illumination option is available. The flow cell (Fig. 1b) patent is owned by WPI [42,43].

Several other detection modes are achievable such as chemiluminescence, fluorescence and Raman spectroscopy with the LCW [17]. Turbidimetric measurements might also be implemented in the LWCCs however these systems should guarantee no accumulation of solids inside the equipment [5].

Based on these characteristics, employing LWCCs in the flow systems, can allow a significant improvement of analytical characteristics of methods that rely on solution phase spectrometry. In addition to its low IR, the gas permeability and hydrophobic properties of Teflon AF enable the development of innovative sensing techniques [17]. It can be used with manual sample injection, as gas sensors (Type I), and for in situ analysis with most liquids (with the exception of perfluorinated solvents).

In spite of the above referred important advantages of LWCCs it is also true that some significant drawbacks are related to them.

The amplification of the blank signal is one of the main drawbacks and causes some limitations in the reagents/reactions selection [5]. This problem can be overcome by using immobilised reagents [44]. The air bubbles, the effect of solids in suspension and RI differences in the sample/reagent zone (schlieren effects) may also give an origin to incorrect signals [5].

It should be emphasised that by increasing the path length of the LWCC a greater risk of bubble formation will occur. Moreover, based on the general considerations derived from the Lambert–Beer law, light attenuation will increase at an increasing distance from the light source (via absorption, scattering and eventual guiding losses) and the lower percentage of light transmittance will require an increased light sensitivity detector, or adjustment of the integration time of the CCD detector. Therefore, a LWCC up to 100 cm might be easier to work with in a flow based analytical system than the 200–500 cm LWCC. These considerations are discussed in detail in Dallas and Dasgupta's review [17] and in the articles referred within.

In the following section, a brief description of some applications of the LWCC using different detection modes will be given. Table 1, summarizes the different flow strategies applied in combination with the LWCC detection mode.

4.1. Molecular absorption spectrophotometric detection mode

The configuration of the commercial flow cell, patented since 1996 [43], with axial location of the light source and the detector, is suited for spectrophotometric applications. Other chemiluminometric or fluorimetric detection cells are based on lab developed flow cell and detector configurations. Most of the published work resorts to the application of type II flow cell, and recent publications of chemiluminometric or fluorimetric detection techniques are much less frequent.

Table 1
Flow configurations applied with spectrophotometric detection using the liquid waveguide capillary cell.

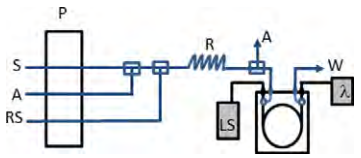
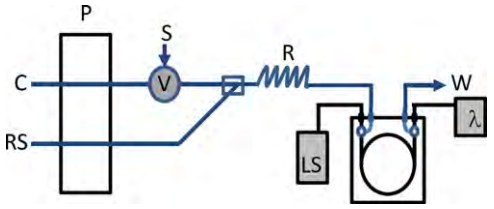
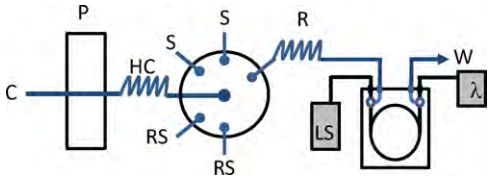
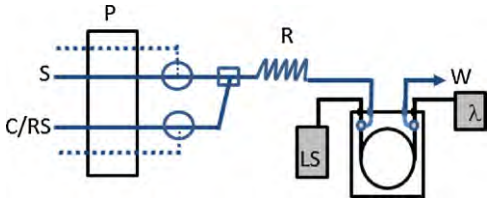
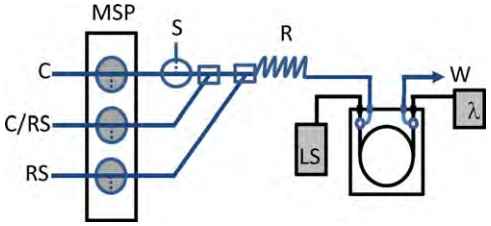
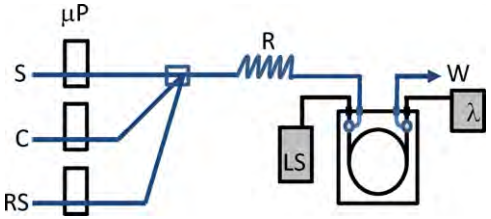
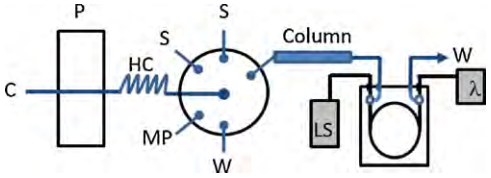
Flow mode	Flow diagram	Principal characteristics	Advantages	Drawbacks	References (LWCC applications)
SFA		First flow analysis technique, segmented flow caused by the introduction of air bubbles in the flow stream with the purpose of: turbulent flow formation, elimination of carry over effects, and prevention of sample dispersion. Steady state measurements achieved	Steady state measurements achieved (advantageous for slow reaction kinetics), widespread commercial expansion	Long response time (2–30 min), high reagent consumption and effluent production	[92–94]
FIA		Laminar flow regime, non-segmented flow, constant volume injection valve applied, reproducible sample injection, controlled dispersion, reproducible timing	Simplicity, short response time (3–60 s), high versatility and sampling rate, easy implementation (no need for computer control), mixing is in most cases promoted by confluences providing constant reagent concentration along the reaction zone	Continuous reagent consumption, effluent production in the mL per assay range, manual operation, difficulties in multiparametric analysis set-up, robustness	[54,73,74,95–101]
SIA		Laminar flow regime, selection valve based flow manifold, reproducible sample injection (programmable flow), controlled dispersion, reproducible timing, mixing is achieved by zone overlapping	Robustness, versatility, lower reagent consumption and effluent production, computer controlled operation, multiparametric operation facilitated	Reduced sampling rate, limited mixing conditions	[102,103]
MCFA		Laminar flow regime, fast switching three-way solenoid valves used for sample and reagent introduction, binary sampling mode, mostly time-based sample injection	Intermittent reagent introduction results in low reagent consumption and effluent production, high sampling rate, computer controlled flow network	Over-heating of the solenoid valves can occur in the absence of electronic protection system, difficulties in handling increased backpressure	[104,105]

Table 1 (*Continued*)

Flow mode	Flow diagram	Principal characteristics	Advantages	Drawbacks	References (LWCC applications)
MSFIA		Laminar flow, multi-syringe device used as propelling and commutation unit, high efficiency in controlling flow rates and sampling volumes	Robustness, low reagent consumption and effluent production, automatic operation, increased chemical resistance, compatible with increased system backpressure	Reduced sampling rate, due to discontinuous pump operation	[49,106–111]
MPFS		Solenoid micro-pumps used as propulsion units and commutation valves, turbulence introduced by pulsed flow,	Low reagent consumption andeffluent production, automatic operation, high portability and versatility, low energy consumption, pulsed flow with improved mixing	Robustness, difficulties in handling increased system backpressure	[46,48–52,111,112]
SIC		Low pressure LC chromatography procedures,	Fast accomplishment of liquid chromatographic procedures, low cost of acquisition and maintenance, low reagent/solvent consumption, potential portability of the system, in comparison with full scale LC	Limited applicability for complex matrix samples, post column dilution deteriorate peak resolution	[89,90]

SFA, Segmented flow analysis; FIA, Flow injection analysis; SIA, Sequential injection analysis; MCFA, Multicommuted flow analysis; MSFIA, Multisyringe flow injection analysis; MPFS, Multipumping flow system; SIC, Sequential injection chromatography; S, Samples/standard solutions; C, Carrier; RS, Reagent solutions; A, Air; R, Reactor; LS, Light source; λ, Detector; W, waste; V, Injection valve; P, Peristaltic or syringe pump; MSP, Multisyringe pump; μP, Micropump; HC, Holding coil.

Interfacing of the LWCC with different flow systems (Table 1) for spectrophotometric detection is a fairly straightforward task. However one should keep in mind that the pressure difference required to provide a steady flow through the analytical system is dependent on the capillary length. In the case of a 1 m capillary cell a flow rate of 1 mL min^{-1} requires approximately 1.5 psi [45]. Therefore flow analysis methods resorting to propulsion unit like peristaltic or syringe pumps have operational advantages over the ones based on solenoid micropumps. This hydrodynamic impedance of the long optical path flow cell will mostly effect the sampling step [46,47]. This drawback can be circumvented by redirecting the flow during the sampling step by means of an extra actuation of valve [46], or by using fixed volume based sample introduction [47] coupled with low reactor lengths and high sample zone volumes.With these considerations the multipumping approaches are viable, and have various advantages in terms of miniaturisation and portability [46–52].

Within the analyte types the detection of metallic cations is one of the most frequent. The analytical characteristics of the developed methods in most cases reach equivalent conditions with the instrumentally demanding alternatives, as can be confirmed by the detection limits of 6 ng L^{-1} for iron [53,54] or 0.4 μg L^{-1} for lead versus the estimated detection limit of 7 μg L^{-1} and 40 μg L^{-1} for plasma emission spectroscopy methods, respectively [55].

Applications of the LWCCs to inorganic and organic analytes in variable matrices using the spectrophotometric detection mode are listed in Tables 2 and 3, respectively. Analytical characteristics like detection limits and application ranges were also compiled. An option was made to try to resume the most prominent novelties of these works within the Notes relative to each included work in the tables. Other published works on more analytical or instrumental aspects of the liquid core waveguides were shortly resumed in the following section. These innovative solutions broaden the possibilities of coupling flow methods with long pathlength spectrometric detection modes.

Dasgupta et al. [30] demonstrated the potential use of LWCC for gaseous analytes; the results obtained confirmed the potential application to CO_2, chlorine, NO_2 and H_2S also the potential to assay volatile organic compounds dissolved in water. Later Milani and Dasgupta [56] developed a method for the differentiation and determination of nitrogen dioxide and nitrous acid using a Type I LWC with various length (7–22.7 cm).

The possibility to detect nanomolar concentrations of metallic species in environmental samples allows studying of oxidative processes via speciation [57,58], and can be carried out without preconcentration processes or without resorting to atomic absorption/emission techniques. This innovative analytical assessment contributes to the better understanding of chemical/biochemical processes occurring at trace concentration levels and their environmental implications.

In situ applications of the LWCC are also increasing in number; the spectrophotometric elemental analysis system (SEAS) [59] using the LWCC detector cell allowed the pH measurement with precision of 0.0014 pH units [60] in the North Pacific Ocean, detection of Cu in estuarine waters with a detection limit of 3 nM [61] in the Bayboro harbour, and the detection of nitrite in deep waters via hydrocast to 200 m in the Gulf of Mexico [62]. Oakes et al. [63] used a LWCC based detection system to monitor and to characterize soluble iron in urban aerosols.

The need to adapt flow cell configurations to specific analytical requirements urged out the in-laboratory development of the LWCC with variable construction/interfacing options. Wang et al. [64] described an autonomous multi-parameter flow system using a LWCC for the simultaneous assessment of pH, carbon dioxide fugacity and total inorganic carbon in seawater. The measurement was based on the colour change of selected pH indicators and it was applied in the surface and underwater monitoring cruise in the western South Atlantic Ocean. Sun et al. [65] constructed an automated analyser using a LWCC for trace nutrients determination in seawater. Robles et al. [66] developed a lab-made LWCC for use in a commercial spectrophotometer applicable to very low light absorbance values for dilute aqueous solutions in both ultraviolet and visible wavelengths. Based on this work Anastasio and Robles [67] applied the LWCC to the determination of soluble light absorbing trace chemical species in Arctic and Antarctic snow.

Another different area of applications of LWCC is based on their incorporation on microfluidic platforms. In microfluidic application the optical path length is one of the most critical limiting factors in reaching low detection limits. Therefore the idea of using total internal reflection detection cells in chip-scale applications is very promising, however the technical difficulties are demanding. Datta et al. [68] used a LWCC impressed in silicon substrates in a chip-scale using Teflon AF. Sun et al. [69] integrated a 1.5 cm LWCC (Teflon AF 2400) into a micro fluidic liquid–liquid extraction system and used this system for sodium dodecyl sulphate determination. Later, Huang et al. [70] developed a micro-FIA system with a 2 cm LWCC (Teflon AF 2400 with 50 μm i.d.) incorporated in the chip and tested for NO_2^- determination (this work achieved consumptions of sample/reagents in the order of nL). In 2010, Pan et al. [71] integrated also the LWCC in a micro fluidic system for DNA measurements.

4.2. Chemiluminescence detection mode

To measure CL emission signals effectively within the short time frame of the monitored reaction either the length of the mixing coil between the last sample/reagent introduction point and the detector (usually a photomultiplier) window must be at its minimum, or the flow rates must be increased resulting in either way in problematic mixing conditions or increased overpressure/and pressure drop. One way to overcome the problem is to carry out the mixing within the viewing volume of the detector (which necessitates large window surface area turning the detector construction more expensive).

Based on the physical configuration of the liquid core waveguide this detector cell can serve both as the mixing and the light-carrying conduit. If the LWCC can effectively collect and transfer much of the CL emission, a high detection sensitivity can be attained with PMTs.

However, for total internal reflection the limitation of the critical angle still to be considered. Only the light emitted in the correct angle will be transported along the cell, adding to this, in chemiluminescent applications the low background absorption of the reagent or carrier stream is of upmost importance, as the increased path length of the cell will increase the absorption of the emitted light by the matrix. This being probably the most critical drawback of the application of chemiluminometric detection techniques coupled to LWCC. Nevertheless, for gaseous analytes successful applications [28,31,72] were published.

Other possible applications can be based on the suppression of chemiluminescence by the analyte. This approach was used to detect salbutamol in pharmaceutical formulations [73] however did not result in improved detection limits (when compared with the existing alternatives).

In a similar approach for hypoclorite detection [74] the authors discuss in detail the self-filtering effect of the used hexacyanoferrate (III) reagent on the generated luminescence. This effect had to be reduced by decreasing the catalyst concentration, and as a result the sensitivity of the CL procedure was hindered.

Table 2
Applications of the liquid waveguide capillary cell with spectrophotometric detection, inorganic analytes.

Analyte	Flow mode	LOD	Linear range	Matrix	LWCC properies	Notes	Reference
Ammonia (NH_3)	MPFS	5 μg L^{-1}	Up to 255 μg L^{-1}	Urban air samples	Type II, AF-2400 (100 cm)	In line capillary membrane diffusion scrubber for air sampling	[112]
Carbon dioxide	Continuous flow	n. g.	Up to 800 μatm $_pCO_2$	Surface seawater	Type I AF-2400 (12 cm)	Autonomous in situ method with low power consumption	[113]
Chloride	Multi-commuted	0.3 mg L^{-1}	Up to 100 mg L^{-1}	Natural waters	Type II AF-2400 (100 cm)	Solid phase reactor with immobilized reagent,	[104]
Chloride	MSFIA	60 μg L^{-1}	Up to 2 mg L^{-1}	Mineral, tap and well waters	Type II AF-2400 (100 cm)	Drastically reduced reagent consumption, 1 mg of $Hg(SCN)_2$ for 3000 Cl^- assay,	[106]
Chlorine	Multi-commuted	7 μg L^{-1}	Up to 1.5 mg L^{-1}	Tap waters	Type II AF-2400 (100 cm)		[105]
Chlorine free (Hypochlorite)	MPFS	6.8 μg L^{-1}	Up to 100 μg L^{-1}	River, lake and tap waters	Type II AF-2400 (100 cm)	With interference studies, EDTA used to inhibit Fe^{3+} and Ca^{2+} effect, hydrodynamic impedance of the LWCC in the sampling step is noticed and avoided by using auxiliary solenoid valve	[46]
Chromium (III) and (VI)	Continuous flow	90 μg L^{-1} for Cr(III) and 0.7 μg L^{-1} for Cr(VI)	Up to 100 mg L^{-1} for Cr(III) and up to 1 mg L^{-1} for Cr(VI)	Aqueous standards	Type I AF-2400 (37.6 cm)	Dual wavelength spectrophotometry, reagent free method with minimal waste effluent	[114]
Copper (II)	MSFIA	0.1 μg L^{-1}	Up to 100 μg L^{-1}	Well, spring, ground and seawater	Type II AF 2400 (100 cm)	Multi-parametric system, (with sequential measurement of Zn)	[111]
Cyanide	FIA	0.8 μg L^{-1}	Up to 260 μg L^{-1}	Air samples and orange, pear and apple seeds	Type I AF-2400 (50 cm)	Different matrixes, blank response eliminated by multi-wavelength measurement	[100]
Iron (II) and (III)	rFIA	6 ng L^{-1} for Fe(II) and 11 ng L^{-1} for Fe(III)	Up to 11 μg L^{-1} for Fe(II) and up to 16 μg L^{-1} for Fe(III)	Rain water	Type II AF-2400 (200 cm)	Speciation based on reduction by ascorbic acid, negligible schlieren effect due to reversed FIA mode	[54]
Iron (II)	Continuous flow	4.6 ng m^{-3}	n.g.	Urban atmospheric aerosols	Type II AF-2400 (100 cm)	Automated instrument for in situ atmospheric monitoring	[115]
Iron	SIA	0.15 μg L^{-1} with ferrozine and 0.35 μg L^{-1} with *o*-phenantroline	Up to 20 μg L^{-1} for both reagents	Ground, sea well, river and potable waters	Type II AF 2400 (100 cm)	Double line SIA method for improved mixing,	[103]
Iron	MSFIA	0.05 μg L^{-1} with ferrozine and NTA superflow resin	Up to 8 μg L^{-1} with ferrozine and NTA superflow resin	River waters	Type II AF 2400 (100 cm)	Solid phase unit (Chelex 100 and NTA Superflow resin), two reagents tested	[107]
Lead	Continuous flow	0.4 ng L^{-1}	Up to 6 μg L^{-1}	River water	Type I; AF-2400 (100 cm)	Mg coprecipitation to remove interferences, blue LED light source used, compact configuration	[116]
Manganese	MPFS	6 μg L^{-1}	Up to1500 μg L^{-1}	River, lake and commercial waters	Type II AF-2400 (100 cm)	Solid phase reactor with immobilized reagent for oxidation, minimized backpressure, reagent lixiviation avoided	[51]
Nitrate (NO_3^-)	FIA	0.12 μg L^{-1}	Up to 9 μg L^{-1} for NO_3^-	Seawater	Type II AF-2400 (200 cm)	An automated instrument for ship board in situ monitoring of open ocean waters, adapted from established standard technique	[96]
Nitrate (NO_3^-)	SFA	93 ng L^{-1}	Up to 37 μg L^{-1} NO_3^-	Seawater	Type II AF-2400 (200 cm)	Automated method, Sulphanilamide-NED, adapted from established standard technique requires no sample pre-treatment Simultaneous parallel measurement of phosphate, salinity matching	[92]

Table 2 (*Continued*)

Analyte	Flow mode	LOD	Linear range	Matrix	LWCC properies	Notes	Reference
Nitrate (NO_3^-)	FIA	93 ng L^{-1}	Up to 12 μg L^{-1} for NO_3^-	Seawater	Type I AF-2400 (16 cm)	Azo compound retained on solid phase (Oasis® HLB cartridge), and eluted in ethanol sulphuric acid mixture, cadmium reduction column required, simultaneous measurement of nitrite	[99]
Nitrite (NO_2^-)	FIA	14 ng L^{-1}	Up to 5 μg L^{-1} NO_2^-	Seawater	Type I AF-2400 (16 cm)	Azo compound retained on solid phase (Oasis® HLB cartridge), simultaneous measurement of nitrate	[99]
Ozone	Continuous flow	0.2 μg L^{-1}	1.5 μg L^{-1}.	Aqueous standards	Type I AF 2400 (130 cm)	Gas sensor, measurements at UV region, reagent free method	[117]
Phosphate (PO_4^{3-})	FIA	0.95 μg L^{-1}	Up to 95 μg L^{-1}	River water	Type II AF-2400 (100 cm)	Molybdenum blue chemistry, Tin(II) chloride reducing agent, interference of silicate eliminated by addition of tartaric acid	[95]
Phosphate (PO_4^{3-})	FIA	0.15 μg L^{-1}	Up to 12 μg L^{-1} for PO_4^{3-}	Seawater	Type II AF-2400 (200 cm)	An automated instrument for ship board in situ monitoring	[96]
Phosphate (PO_4^{3-})	Continuous flow	20 μg L^{-1}	Up to 800 μg L^{-1}	Aqueous standards	Type I AF-2400 (30 cm)	Lab made flow cell	[118]
Phosphate (PO_4^{3-})	FIA	17 μg L^{-1}	Up to 500 μg L^{-1}	Surface and ground waters	Type II AF-2400 (100 cm)	Vanadomolybdate yellow chemistry, stable reagent, low wavelength for monitoring, interference of silicate reduced by the addition of tartaric acid	[97]
Phosphate (PO_4^{3-})	SFA	76 ng L^{-1}	Up to 57 μg L^{-1} for PO_4^{3-}	Seawater	Type II AF-2400 (200 cm)	Automated method, Adapted from established standard technique, molybdenum blue chemistry, requires no sample pre-treatment Simultaneous parallel measurement of nitrite/nitrate, salinity matching	[92]
Phosphate (PO_4^{3-})	rFIA	47 ng L^{-1}	Up to 16 μg L^{-1}	Seawater	Type II AF-2400 (200 cm)	Reversed flow method, molybdenum blue chemistry, low reagent consumption	[98]
Plutonium (PuO_2^{2+})	Continuous flow	110 μg L^{-1}	Up to 27 mg L^{-1}	Aqueous standards	AF-2400 (100 cm)	Spectral changes for the stability studies of Pu(VI) species	[119]
Silicate (SiO_3^-)	SAI	8 μg L^{-1}	Up to 7.6 mg L^{-1}	Surface seawater	Type II AF-2400 (200 cm)	The salinity effect was studied and different length of LWCCs were tested	[102]
Silicate (SiO_3^-)	FIA	0,8 μg L^{-1}	Up to 380 μg L^{-1}	Seawater	Type I AF-2400 (160 cm)	Phosphate interference eliminated by oxalic acid; no salinity interference noticed	[101]
Silicic acid	SFA	1 μg L^{-1}	Up to 192 μg L^{-1}	Seawater	Type II AF-2400 (100 cm)	In situ ship board measurements,	[94]
Sulphate (SO_4^2)	Multi-pumping	150 μg L^{-1}	Up to 16 mg L^{-1}	River and rain waters	Type II AF-2400 (100 cm)	Turbidimetric determination, periodical washing step with EDTA included	[48]
Thorium (IV) and Uranium (VI)	MSFIA combined with LOV	5.9 ng L^{-1} for U and 60 ng L^{-1} for Th	Up to 1.2 μg L^{-1} for U and up to 2 μg L^{-1} for Th	Fresh, mineral, tap, well and seawater	Type II AF 2400 (100 cm)	Solid phase unit (UTEVA resin), fully automated system	[109]
Titanium (IV)	MPFS	0.4 μg L^{-1}	Up to 100 μg L^{-1}	Estuarine,sea, river, mine and well waters	Type II AF 2400 (100 cm)	Interference studies, applied to a lake sediment and sunscreen formulations	[47]
Uranium (VI)	MPFS combined with MSFIA	12.6 ng L^{-1}	Up to 0.155 μg	Fresh, mineral, tap and seawater	Type II AF-2400 (100 cm)	Solid phase unit (Transuranide resin),	[49]
Uranium (VI)	LOV with MSFIA	10.3 ng L^{-1}	Up to 0.3 μg	Sea, well, fresh, tap and mineral waters	Type II AF-2400 (100 cm)	Solid phase unit (UTEVA resin)	[108]
Zinc (II)	MSFIA	2 μg L^{-1}	Up to 100 μg L^{-1}	Well, spring, ground and seawater	Type II AF 2400 (100 cm)	Multi-parametric system (measurement of Cu(II))	[111]

Table 3
Applications of the liquid waveguide capillary cell with spectrophotometric detection, organic analytes.

Analyte	Flow mode	LOD	Linear range	Matrix	LWCC properties	Notes	Reference
Carbaryl	MPFS	1.7 μg L^{-1}	Up to 200 μg L^{-1}	Natural waters	Type II AF-2400 (100 cm)	Sample clean-up by cloud-point extraction, with waste treatment	[50]
Glyphosate	MPFS	0.2 mg L^{-1}	Up to 10 mg L^{-1}	Commercial, spring and river waters	Type II AF 2400 (100 cm)	Derivatisation reaction for visible wavelength monitoring, interference studies for saline components, amine group containing analytes, and metabolites	[52]
Nitrophenols	Continuous flow	12–60 ng L^{-1}	n.g.	Rain water and air	Type I AF-2400 (142 cm)	Solid phase unit (anion exchanger), reversed phase separation column, chemically active liquid core waveguide detector cell	[120]
Paraquat	MSFIA	0.7 μg L^{-1}	Up to 250 μg L^{-1}	Commercial water	Type II AF 2400 (200 cm)	Visible wavelength (610 nm), automated standard addition pocedure, interference study for major saline components, and other "quat" herbicides	[110]
Triazine herbicides (simazine, atrazine, and propazine)	SIC	2.3 μg L^{-1} for simazine, 1.9 μg L^{-1} for atrazine, and 4.5 μg L^{-1} for propazine,	5–200 μg L-1	Tap and river water	Type II AF-2400 (100 cm)	25 mm C18 monolithic column, interference of humic substances noticed at UV range detection wavelength, high attenuation of the light beam at UV wavelength	[89]
Veterinary drug residues (Toltrazuril and lasalocid)	SIC	19 μg L^{-1} for toltrazuril and 10 μg L^{-1} for lasalocid	Up to 1 mg L^{-1} for toltrazuril and up to 2 mg L^{-1} for lasalocid	Ground and commercial waters, pharmaceutical formulations and feed samples	Type II AF-2400 (200 cm)	Monolithic column C18, UV detection at two different wavelength;	[90]

Table 4
Deviations from the expected sensitivity increase derived from the Lambert–Beer law (comparison of the experimental conditions).

Flow system	Chemistry involved	Wavelength	Deviation from the expected sensitivity increase	Reference cell configuration	LWCC configuration	Notes	Reference
FIA (double line)	Permanganate (no chemical reaction)	617, 700 and 800 nm	+0.2%	1 cm (quartz cell 80 μl nominal volume	100 cm, Type II		[5]
FIA (double line)	Cr (VI) Diphenylcarbazide	617, 700 and 800 nm	−20%	1 cm (quartz cell 80 μl nominal volume	100 cm, Type II	Dispersion effect claimed, D_{LWCC} = 2.7 versus D_{RC} = 2.1 for a 150 μL sample volume	[5]
FIA (3 line)	Phosphate (molybdenum blue method)	660 nm	+1.3%	1 cm (80 μL nominal volume, 0.3 cm i.d. quartz cell)	30 cm, Type I, (internal volume 75 μL)	Sample volume 250 μL	[118]
FIA (3 line)	Phosphate (vanadomolybdenum yellow method)	380 and 446 nm	−89%	1 cm (30 μL inner optical volume)	100 cm, Type II	Different wavelength used in the two set-ups, higher molar absorptivity at the wavelength (380 nm) used with the 1 cm cell.	[97]
MCFA (double line)	Solid phase reagent (Silver chloranilate)	530 nm	−25%	1 cm	100 cm, Type II	Radiation power attenuation claimed, ~80 μL sample volume,	[104]
MPFS	Turbidimetric sulphate determination	410 nm	−70%	1 cm (80 μL nominal volume, 0.3 cm i.d. quartz cell)	100 cm, Type II	Attenuation of the radiation power by light scattering is claimed and the effect of the lower sulphate concentration on the initial nucleation rate (kinetic effect)	[48]
MPFS	Manganese	490 and 750 nm	+20%	1 cm (80 μL nominal volume)	100 cm, Type II	Higher oxidation efficiency achieved for more diluted Mn solutions (kinetic effect)	[51]

D_{LWCC} and $D_{RC:}$ dispersion coefficients for the LWCC and reference conventional flow cell.

4.3. Fluorescence detection mode

Similarly to what happens in a chemiluminescent reaction, a fluorescing molecule in the flow cell will radiate light isotropically. Based on the low critical angle, the fraction of light transported/collected in the axial direction is also low. Additionally, care must be taken when designing the detector set up to prevent the excitation light from reaching the detector [17]. Therefore, transversely illuminated and axially collected light based set ups are the most frequently applied. Capillary cells are normally shorter (<50 cm) to avoid extensive light absorption by the reaction media. Beside these limitations, the applications of LWCC with fluorescence detection described in this section present several advantages when compared to commercial fluorometers such as, low price, similar detection limits, uncomplicated operation mode and versatile configurations.

Fujiwara et al. [75] constructed a model for estimating the probability of a photon to reach the end of the capillary cell, and studied the effect of the solvent refractive index and the excitation wavelength on the fluorimetric properties of the waveguide. They concluded that a 10 times enhancement on the detection capability can be achieved, if non ultraviolet excitation wavelength is used, and the excitation is executed through the capillary while the generated fluorescence is detected from the vertical side of the waveguide cell. This configuration is fundamentally different from the one used by the research group of Dasgupta and co-workers [76,77], where transverse excitation and axial detection is applied. This group has published various papers on successful fluorimetric detection systems with LWCC for gaseous analytes [78,79]. By taking advantage of the gaseous media, the background absorption problem was minimised. Based on the same optical arrangement, Byrne et al. [80] constructed a compact spectrofluorometer with wavelength discrimination capabilities and tested it for seawater fluorescence measurement.

Other application possibilities are based on the coupling [81] of the LCW to the separation capillaries used in the electrophoresis process. Small dimension (1 cm length) detection zone on the LCW allowed the post column [82] or even on-column [83,84] detection of fluorescent labelled amino acids. The results showed detection limits approaching those of chip-based capillary electrophoresis systems employing much more sophisticated optics. Other similar examples can be found for the electrophoretic separation and fluorimetric detection of DNA fragments [85–87].

The LWCC was also tested for liquid chromatography in flow analysis systems by Song et al. [88]. This study revealed the potentiality of LWCC to be applied in non-electrophoretic separation processes coupled in series with other detectors.

5. Conclusions and future trends

Despite of its relatively recent development and on the somewhat limited commercial availability, liquid waveguide capillary cells has gained popularity in the past decades in the area of analytical chemistry. Some of the referred limitations are summarised in the following points:

- There is an increased susceptibility to interferences due to the increased sensitivity; effective elimination/masking of the interfering agents requires careful optimisation of the chemical parameters of the flow system; an effective way of eliminating interferents in the ppm concentration ranges might not be sufficiently selective in the low ppb ranges.
- The dispersion phenomena in a LWCC differ from the conventional flow cells. Transposing a flow method with a conventional flow cell to a LWCC based detection mode might change the mixing conditions considerably. Small diameter capillary with increased length results in internal cell volumes up to 1.25 mL that can be significantly different than the corresponding 1 cm pathlength U or Z shaped flow cells. This dispersion effect, in our wiew, should be quantified in every applications where the comparison of the detector cell configurations and lengths are in concern.
- Background absorption of solutions/reagents causes limitation in absorption measurements, especially at lower wavelengths (UV). Charge coupled device based spectrophotometric detectors have increased sensitivity for low light conditions and this makes them especially attractive for these type of applications. In case of the chemiluminometric or fluorimetric detection modes, the viable increase in pathlength is mostly limited by the factor of self-absorption. Strategies that are based on the quenching of the fluorimetric/chemiluminometric signal or on the decolouration of reagent solutions will most probably not benefit from the increase of the pathlength. However, the easy coupling to the detector via optical fibres and to electrophoresis separation capillaries still holds some possibilities for improvements of the analytical characteristics (robustness in miniaturisation) of these methods.
- In spectrophotometric applications of the LWCC the increase in the sensitivity sometimes is different from the theoretical values expected from the Lambert–Beer law. (Table 4) It could be concluded that in these cases experimental conditions do not agree within the alternatives compared, so the solemn contribution of the increase in the light path is difficult to isolate. However, some possible explanations were suggested in the literature. In the case of positive deviations (higher sensitivity found than it is expected from the increase in cell length) the lower analyte concentrations results in higher excess of the reagents, and this excess can affect the kinetics and the extension of the involved reactions [51]. Negative deviations (beside the already mentioned alterations in the physical dispersion) can be the result of UV range measurements where the type II cells can present a shorter effective optical pathlength than the physical length of the cell [35]. The low analyte concentrations will also affect the initial nucleation rate in turbidimetric measurements, resulting in a lower than expected sensitivity increase [48]. In the specific case of SIC methods the cell internal volume will significantly increase the post-column dilution of the eluted analyte and this way deteriorate the peak resolution of the method. In practice, this will result in the need to re-optimise the injection and elution conditions [89,90], therefore the sensitivities obtained cannot be compared directly.
- For flow methods there is another factor that can limit the application: the pressure difference required to provide a steady flow through the analytical system is dependent on the capillary length. In the case of a 1 m capillary cell, a flow rate of 1 mL min^{-1} requires approximately 1.5 psi. This also implies that the dynamic viscosity and density of the solutions can influence the repeatability of the analytical signal if not the most appropriate liquid drive is chosen.
- Pre-filtering solutions entering the flow cell can be a time consuming protocol but it is worth to consider, not merely because of the internal diameter of the capillary (0.55 mm) but also because of the two lower dimensions “bottlenecks” in the T-junctions used in the interface of the liquid capillary with the fibre optic cable. Removing a trapped solid particle from the flow cell is certainly a difficult and troublesome process.

Despite of these accepted and well known limitations, the improved sensitivity and detection limit is an important feature. Interfacing of these cells with automated liquid handling flow methods improve also the repeatability, precision and portability

of the developed methods, opening the perspectives of areas like environmental chemistry to problems where trace analyte concentrations have to be assessed.

New materials will most certainly be developed with low refractive indexes, and their application as cladding or wall materials can bring additional advantages in the development of miniaturised systems. Functionalised wall surface can serve as a basis for the development of optical sensor systems.

As it can be concluded from the variety of the analytes discussed in this report the chemistry to be applied cannot be a limiting factor in the development of analytical methods. In our view, future effort should be focused on the development of portable or in situ instruments based on this detection cell. The relatively easy interfacing of the capillary cell with the detector and the light source via optical fibres, promotes the development of miniaturized systems.

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