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REVIEW ARTICLE

A comprehensive review of liquid chromatography hyphenated to post-column photoinduced fluorescence detection system for determination of analytes

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Abstract Liquid chromatographic separation technique coupled with fluorescence detector (LC-FLD) has been one of the primary sensitive and selective analytical techniques in various science areas including environmental, food, biological, biomedicine etc. Its significance relies on several analytical advantages including cost-effectiveness, enhanced sensitivity, and selectivity performance. However, the desired applications of this technique and detection limits are not always possible without target analytes derivatization. When analytes manipulation is carried out by mere

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Hyphenated system;
Summaries of applications

light, the mechanism is called photoderivatization or photochemical reaction. This addition of photochemical reactor has significantly enhanced the LC-FLD capability for selective, sensitive, and reproducible determination of variety of analytes such as pesticides, pharmaceutical drugs, flavonoids, vitamins etc. as compared to chemical pre/post-column derivatization. Herein, we have comprehensively and systematically summarized the development, instrumentation and applications of liquid chromatography-photoinduced fluorescence technique (LC-*hv*-FLD) to analyze a large number of analytes-residues in various matrices published between the years i.e., 2000 to 2022 along with some outstanding and important contributions before this time span. Moreover, the essential characteristic, advantages/disadvantages, challenges, and future prospects have also been highlighted. We expect this manuscript to be a useful key reference for the future development in fluorescence based chromatographic analysis and inspire new ideas and discoveries in the direction of reagent-less and online derivatization of intrinsically non-fluorescent analytes.

1. Introduction

Liquid chromatography (LC) techniques in combination with cost-effective, selective and sensitive fluorescence detection system have attracted significant attention to determine wide range of analytes in separation science. However, this sophisticated and efficient combination doesn't always yield desired results due to its poor sensitivity towards a large number of fluorescence inactive analytes. This phenomenon is linked to the lack of fluorophore for fluorescence or chemiluminescence detection, chromophore for UV–Vis detection and electrophore group in analytes for electrochemical detection (Lores et al., 1999, Jones et al., 2015, Natalia and Constantinos, 2019). A wide range of compounds, despite possessing a certain degree of necessary aromaticity, are not fluorescent active. Therefore, the successful application of liquid chromatography combined with fluorescence detector (LC-FLD) to determine non-fluorescent analytes to obtain desire detection limit with good precision is not possible without necessary analytes-manipulation or derivatization. Although, it's often named as a "necessary evil" but this procedure helps to convert non-fluorescent analytes into their detectable form for their sensitive and selective determination along with minimizing or eliminating the matrix interferences effect (Jones et al., 2015, Ji et al., 2019, Luo et al., 2019a, 2019b, Natalia and Constantinos, 2019).

Naturally fluorescent compounds can be analyzed directly without any manipulation, however, if the compounds exhibit weak or no fluorescence response then these can be turned into their respective fluorescent forms by using different physicochemical derivatization methods including photochemical reactions. This mode of derivatization provides a new route for many non-fluorescent aromatic compounds having one or more photo scissor-able functional groups that can help convert these types of analytes into more stable and fluorescence active derivative forms to ensure their sensitive analysis (Lores et al., 1999, Jiménez-López et al., 2019a, 2019b). Similarly, a number of fluorometric and derivatization methods are introduced to transform intrinsically non-fluorescent compounds into their respective fluorescent derivatives as elaborated below and also depicted in Fig. 1.

In direct fluorometric methods, the simple liquid chromatography-fluorescene (LC-FLD) technique can be used directly for the fluorescent determination of analytes exhibiting sufficient intrinsic fluorescence intensity. Therefore, many analytes of different classes such as anticoagulant rodenticides, carbamate insecticide, pesticides, herbicide, fungicides, some organophosphorus insecticides and pharmaceutical drugs are naturally fluorescent active that falls in this category (Muhammad et al., 2021). There are few other direct fluorescent analysis methods but their routine application is obsolete. For instance, silica gel plates are inexpensive solid substrates but lacks selectivity and sensitivity. Similarly, fluorimetry in bulk analytes solution is another method for their enhanced and selective determination by using first or second derivative spectra spectrofluorimetry. Hence, among these only HPLC-FLD has appeared as method of choice for the trace determination of compounds. But the number of compounds exhibiting intrinsic fluorescence are rather limited (Coly and Aaron, 1994a, 1994b, Hillebrand et al., 2002, Flores et al., 2007a, 2007b, López-Flores et al., 2007a, 2007b, Poole, 2017, Muhammad et al., 2018a, 2018b, 2018c).

In this view, there are various indirect or pretreatment methods are being used to transform weakly or non-fluorescent analytes into their intensely fluorescent components. Most of these methods involve generation of fluorophore by means of appropriate pretreatment such as chemical reagent treatment; heat treatment; fluorogenic labelling; complexation reactions or photochemical derivatization (Muhammad et al., 2017, Poole, 2017).

Among these fluorescence pretreatment methods, LC derivatizations are categorized in two main types namely pre-column derivatization and post-column derivatization (PCD) depending upon the nature of analytes and reaction system to improve fabricated system sensitivity and selectivity for the reliable estimation of target analytes (Ibrahim et al., 2010, Zacharis and Tzanavaras, 2013). Purpose of each of these derivatization modes is to enhance the detectability of extrinsically fluorescent analytes, stabilization of samples, and to ensure compatibility and separation with selected analytical technique (Pérez-Ruiz et al., 2004, Zacharis and Tzanavaras, 2013, Jones et al., 2015, Yu et al., 2019a, Yu et al., 2019b, Gunnarson et al., 2021). Most of these derivatization methods involve addition of chemical reagents for the conversion of that particular analytes through acylation, esterification, dansylation, silylation etc. into its respective fluorescent active form (Poulsen and Birks, 1989, Lores et al., 1999, Luo et al., 2019a, 2019b, Yu et al., 2019a, Yu et al., 2019b, Gao et al., 2020, Wang et al., 2020, Tsiasioti et al., 2021).

Among these, photochemical derivatization is a reagent-less approach to turn non-fluorescent analytes through an appropriate structural change such as isomerization, rearrangements, dimerization's, photohydrolysis, photolysis, and so on into their respective fluorescent. This reagent-less derivatization approach is a superior alternative to classical chemical reactions-based approaches. In photochemical derivatization approach the use of electromagnetic irradiation not only makes it environment friendly but also significantly minimizes the creation of waste products. Moreover, the light doesn't cause interfering residues and stability problems in comparison to chemical derivatization reactions. Photochemical reactor can help to characterize the photo-degradation phenomenon of target non-fluorescent analytes. It uses simple, and flexible instrumentation as compared to reagent-based methods (post-column pump, mixing coils) as detailed chromatography-photoinduced fluorescence detection system configuration (LC-*hv*-FLD) and its comparison with chemical derivatization based derivatization is elaborated in Fig. 2 **(a & b)** (Stewart, 1982, Stewart and Bachman, 1988, Lores et al., 1999, Schmidt, 2003, Zacharis and Tzanavaras, 2013).

Therefore, this paper aimed to comprehensively review the instrumentation and applications of liquid chromatography hyphenated to simple post-column photochemical reaction systems for sensitive fluorescence determination of analytes of all classes. According to best of our knowledge, it is the first review covering around 22 years of scientific literature (Fig. 3**(a)**) for the comprehensive survey on the use of this non-conventional IC-*hv*-FLD technique for the sensitive determination of different analytes (organic & inorganic). To draw its comparison with other chemical/physical derivatization methods, its significance, limitations and applicability were also highlighted for better conclusion. It's worth to highlight that the fundamental aspects show only small fractions of the problems typically required to be resolved during the improvement of the LC-*hv*-FLD method. All classes of analytes that being analyzed by using LC-*hv*-FLD technique are described separately and their respective detailed information summarized in up-to-date table with the goal of providing readers a trend and idea to explore this approach in other field of analytes and sample metrics.

2. Photochemical derivatization and instrumentation

Photochemical derivatization (PD) similar to classical chemical derivatization is also classified into two main types' pre-column and post-column photochemical derivatizations. Fundamentally, both of these procedures are used to introduce fluorophores having higher fluorescence response and to improve the selectivity by specific derivatization of target analytes for their determination in complex matrix. The photochemical derivatization is applicable to only limited and particular kind of analytes having specific molecular structure that have ability to absorb UV irradiation (Burrows et al., 2002, Osorio et al., 2014).

The pre-column PD is further categorized in offline and online PDs. In offline PD the sample containing target analytes are transferred into a transparent quartz cuvette and placed into UV cross-linking instrument for period of time for their conversion into fluorescent form. Whereas, in online mode the photochemical reactor is placed just before the separation column for the rapid formation of respective fluorescent products. The offline pre-column PD is needed when the photodegration time of analytes is too long, while online pre-column PD used when the characterization of the photoproducts is of interest. This could provide critical new information about the mechanism of photochemical reactions for improving the analytical method. However, this mode of derivatization is scarcely being used as compared to post-column PD (Brinkman, 1987, Lores et al., 1999, Parlar and Surmann, 2000, Mughari et al., 2007, Osorio et al., 2014, Liu et al., 2016). In post-column PD derivatization, the photochemical reactor is placed after the separation column and before the detector for the rapid conversion of non-fluorescent into their

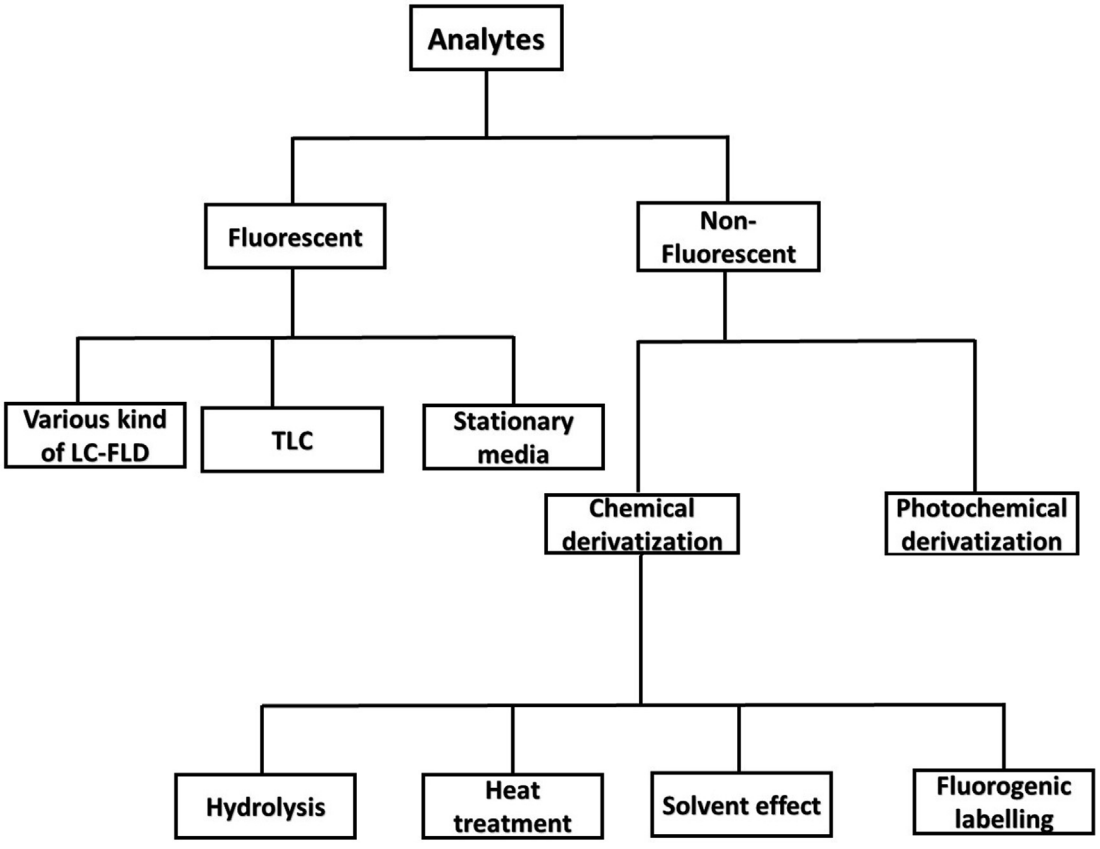

Fig. 1 Schematic view of the various fluorescence approach for analysis of analytes.

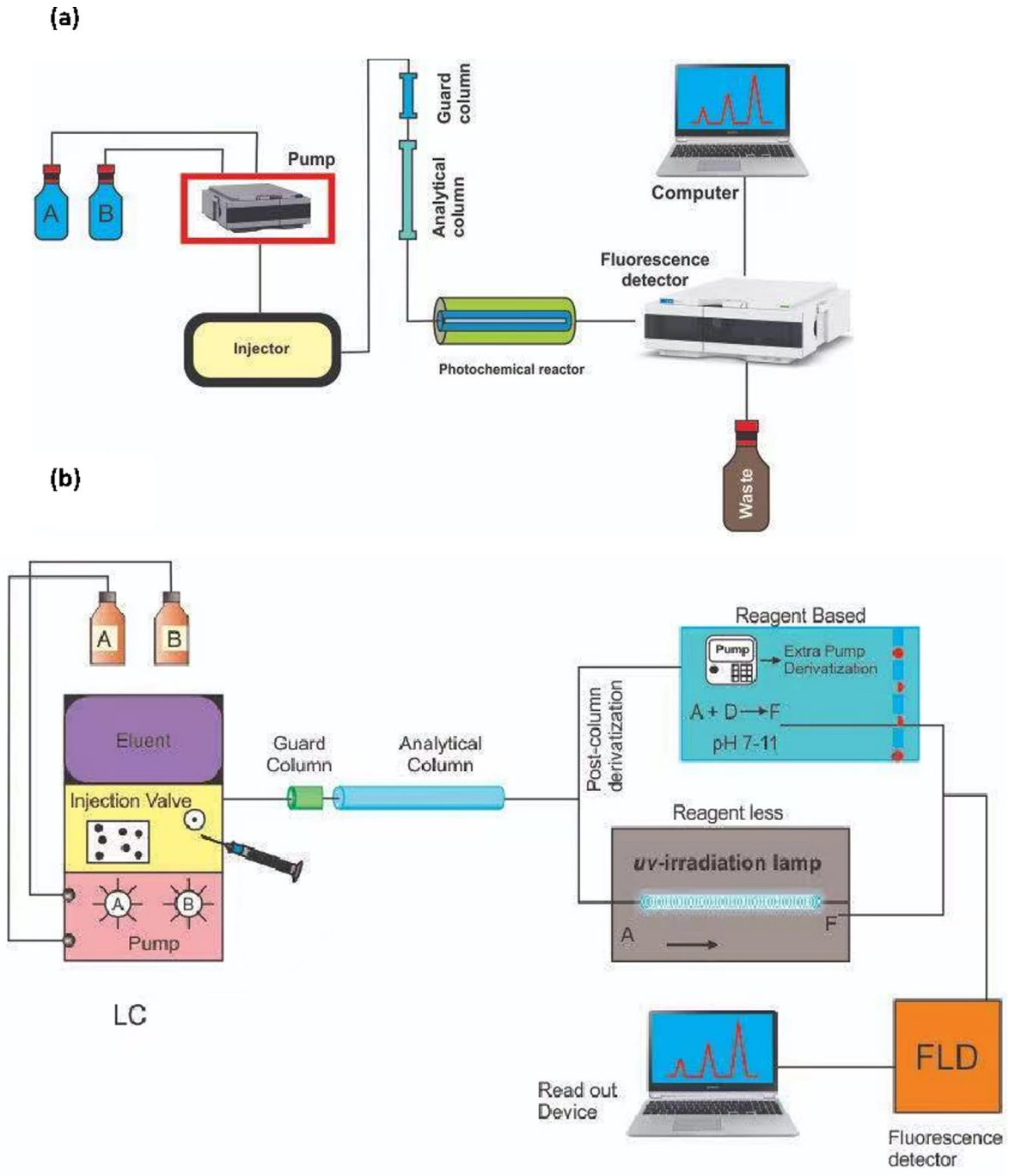

Fig. 2 Systematic diagram of (a) liquid chromatography coupled with post-column uv irradiation fluorescence detection system; (b) comparison of post-column reagent-based and UV irradiation-based derivatization.

respective fluorescent form. The detailed comparison of pre-column and post-column PD advantages and disadvantages is delineated in **Table S1.**

2.1. Instrumentation of liquid chromatography-photoinduced fluorescence technique (LC-hv-FLD)

The primary difference between conventional LC-FLD and LC-*hv*-FLD techniques is the photoreactor. Photochemical reactor is the reagent-less and pump-less system and a critical component of LC-*uv*-FLD technique, which makes its instrumentation simpler as compared to reagent-based technique as shown in Fig. 2**(a)**. Sometime this is also used for the acceleration of chemical reaction occurring in chemical-based derivatization procedure. The increasing demand of photochemical reactors in wide range of applications has encouraged its commercial manufacturing by well-known trade-mark such as UVE™, PHRED™, Beam-Boost™, and Photoblaster™ (Stewart, 1982, Stewart and Bachman, 1988, Lores et al., 1999, Parlar and Surmann, 2000, Schmidt, 2003, Molina-García et al., 2011, Zacharis and Tzanavaras, 2013).

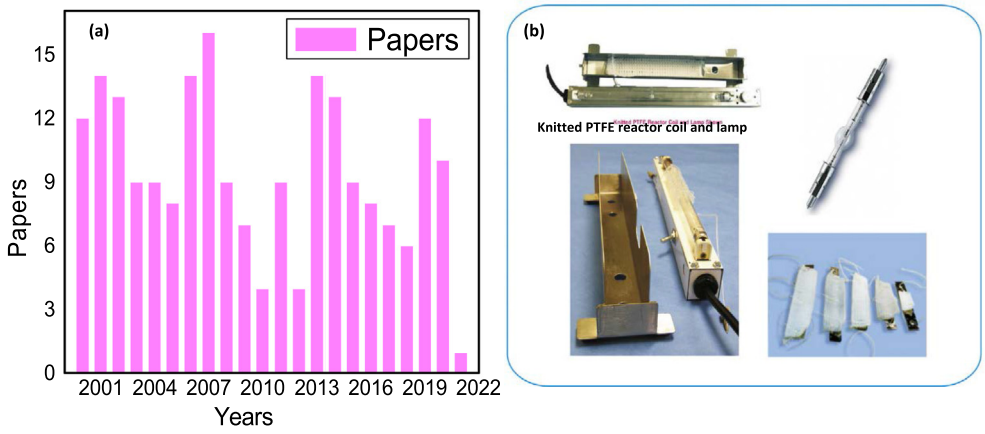

Fig. 3 Systematic diagram of (a) number of studies reported per year from 2000 to 2022. (b) lamps and knitted reactors; (Fig. 3 (b) reprinted from Luo et al., 2019a, 2019b with permission from Elsevier.

2.1.1. Classification of photochemical reactor

The main purpose of post-column photochemical reactor in most of the chromatographic techniques is to turn-on the non-fluorescent analytes for their sensitive determination in complex samples. The photochemical reactor is comprised of irradiation source (mercury, xenon, or xenon-mercury lamp) knitted by the particular kind of reaction coils to assure maximum transparency to the UV light to ignite photochemical reaction. Photochemical reactors had been categorized in three main types on the basis of kinetics of photochemical reaction namely (i) open-tubular (ii) packed-bed and (iii) segmented-stream reactors (Brinkman, 1987).

Open-tubular is a simple and commonly used reactor as it is fabricated by coiled, straight or by intertwining piece of glass, steel of PTFE tubing around the selected lamp. The tubing is normally knitted or coiled to reduce band broadening that arises due to phenomenon of secondary flow. This reactor is normally applied for fast kinetics reaction having residence times between 30 and 60 s. The packed-bed reactors composed of glass or stainless-steel columns with packing of small inert, non-porous glass beads having p.s 10–15 μm diameter and these reactors are commendable in terms of mixing and band broadening for those chemical processes which have intermediary reaction times of around 0.5 – 4.0 min. Finally, the segmented-stream reactors are used for the analytes that require slow kinetic reactions with residing time of more than 4 min. However, this reactor has a complex configuration and the need of segmentation can cause band broadening and eventually poor sensitivity (Brinkman, 1987, Scholl et al., 1987, Brinkman et al., 1989, Milofsky et al., 2000).

2.1.2. Classification of reaction coils

Studies have found that light-tubes having characteristics of radiation diffusion and internal reflectance play an important role to control the flux of effective photon for the photo transformation of target analytes (Scholten et al., 1980). Based on this principle, there are two different reaction material namely Polytetrafluoroethylene (PTFE) coils and Pyrex glass have been investigated considering most of analytes have absorption maximum below 300 nm. It was observed PTFE material coil appeared better choice because of its ability to maximum transmission of UV light below 30 nm, apart from entailing improved and symmetrical peaks than quartz capillaries. Moreover, fluorinated ethylene propylene tubes are more flexible, durable and exhibit more than 90% UV transparency (Scholten et al., 1980, Poulsen et al., 1986). Whereas, pyres glass coils suffer various limitations such as poor ignition of photochemical reaction even with UV irradiation having $\lambda > 300$, high cost, fragility, and unavailability in different geometries (helix, coil, etc.). The PTFE tube various characteristics such as low cost, ease of installation, readily availability, transparency to UV radiation (in range of 230 – 400 nm), resistance to oxygen permeability to avoid photo-oxidation reactions and its narrow bore tubing ability to reduce dead volume and band broadening not only enhances PIF intensity but also decreases analytes residence time up to 18 – 20 s for their maximum transformation as compared to Pyrex glass coils (Scholten et al., 1980, Poulsen et al., 1986, Rigas, 2012, Zacharis and Tzanavaras, 2013, Acebal et al., 2014). An example of a photoreactor made with this advantageous PTEF coil is depicts in Fig. 3**(b).**

2.1.3. Factors affecting the photochemical reaction

The photochemical reaction efficiency for any target analytes is governed mainly by following parameters.

I. Irradiation source
II. Irradiation time
III. Types and configuration of photo reactor
IV. Nature of medium and pH
V. Effect of nature of solvents

The light source is most important part of photoreactor and it is normally chosen by taking into account the requirement of wavelength and intensity of irradiation for particular group of analytes. There are different kind of irradiation source have been used for online photoderivatization viz: xenon, mercury, hydrogen, deuterium lamps. Besides, germicidal, fluorescent, incandescent, and pencil lasers or combination of two different lamps have also been tested in photochemical reactors. Generally, PIF intensity increases as the irradiation time gradually increases, after reaching the optimum values this trend is reversed. For instance, diflubenzuron and fenvalerate PIF intensity continue to increase with the increase of irradiation time with no maximum value achieved. This can be related to the slow kinetics of this single step photolysis reaction

(Coly and Aaron, 1994a, 1994b, Rocha et al., 2015). Similarly, chlorpyriphos also follow similar pattern in the presence of β-fcyclodextrine, its PIF intensity continues to increase with time and eventually levels off. This is due to establishment of equilibrium between its dechlorinate photoproduct and degradation products (Coly and Aaron, 1998). In conclusion, the irradiation lamp and intensity play pivotal role to govern the detection, selectivity and sensitivity (Icardo and Calatayud, 2008, Farokhcheh and Alizadeh, 2014, Rocha et al., 2015).

The irradiation time for the online derivatization can be easily adjusted by variation of length of tubing knitted around photoirradiation lamp and flow rate. These parameters can influence the analytes separation and result in peaks broadening, poor resolution, low throughput, and high LOD values are few of them (Coly and Aaron, 1999, García-Campaña et al., 2001). Small diameter tubes in the range 0.2 to 2 mm (I.D) are most feasible choice to obtain analytes separation with better analytical parameters viz, better peaks resolution, minimum peak broadening (Poulsen et al., 1986, Calatayud, 1996, López-Flores et al., 2007a, 2007b, Icardo and Calatayud, 2008).

The photoreaction medium can influence the formation of photoproducts and their PIF intensity. The reaction media based on polarity are classfied into two types: protic and non-protic. For instance, the diflubenzuron and deltamethrin exhibit higher PIF signals in protic solvents such as binary mixture of water with methanol/ethanol/acetonitrile (Parrilla Vázquez et al., 2005). Similarly, cetyltrimethylammonium chloride (CTAC) in water significntly increases the PIF signal of 2,4-dichlorophenoxyacetic acid herbicide by a factor of 30.9 (-García-Campaña et al., 2001). In addition, the reaction medium pH and nature of used solvents also govern the overall effectiveness of UV irradiation. The organic analytes absorption and fluorescence characteristic varies as excitation intensity increases due to change in photochemical and photophysical properties of the target molecule. For instance, at normal conditions phenols in aqueous media don't absorb any low intensity XeCl radiations. But by using mercury lamp at $\lambda = 365-405$ and 435 nm, phenols in ionic form (basic pH) exhibited higher photoproduction rate at the absorption bands around 41,000 cm^{-1}. This formation of photoproducts enhanced the absorption intensity of ionic phenols around 240 nm. Besides, basic pH also facilities the dimerization of anionic analytes under UV irradiation as a result absorption intensity increase (Tchaikovskaya et al., 2000, Gatti et al., 2001). Similarly, carbendazim doesn't undergo photodegradation in acidic condition (pH = 1), but in alkaline media the photodegradation rate increases with the rise in pH. This phenomenon can be delineated by the fact that in alkaline media carbendazim loses proton immediately and the formation of 2-aminobenzimidazole takes place easily under UV irradiation as shown in scheme of **Figure S1.** Whereas, at low pH benzimidazole ring gets protonated, which is stable under UV irradiation in contrary to high pH (Panadés et al., 2000, Mazellier et al., 2002).

Finally, solvents in separation or reaction media play crucial role in controlling the overall PIF intensity of target analytes. For instance, flufenamic acid is a non-steroidal anti-inflammatory medicine that exhibits weak fluorescent intensity in ethanol but yields stronger fluorescence signals in acetonitrile, dioxane and dimethyl sulfoxide (DMSO). It appeared both fluorescence excitation and emission spectra of flufenamic acid are only impacted by polarity of dioxane and results in 20 nm blue shift in emission spectra. This analyte PIF signal intensity is affected significantly with the variation of solvents. For example, its maximum emission appeared at shorter wavelength in DMSO and dioxane than in aqueous media or ethanol. This phenomenon can be attributed to the formation of different photoproducts in different solvents of that particular analyte (Bettaieb and Jean-Jacques, 2001).

2.2. Advantages and disadvantages

i. The on-line photochemical derivatization when compared to chemical derivatization is simple and offer multiple advantages to convert weakly or non-fluorescent analytes into strongly fluorescent photoproducts such as no addition of reagent/auxiliary post-column pumps, simple construction of photochemical reactor, fast kinetics of photochemical reactions, no or minor artifact impurities, highly reproducible results, don't degrade pump or other part of instrument, and enhance the absorption coefficient and quantum yield of resulting fluorescent analytes (Mellinger and Keeler, 1964, Scholten et al., 1980, Birks and Frei, 1982, Frei, 1982, Brown et al., 1983, Gandelman et al., 1983, Scholl et al., 1987, Mbaye et al., 2009)..
ii. Fluorescence detector when compared to other spectrophotometric detection strategies are comparatively selective, and able to overcome matrix interference, because only limited number of analytes or species are in a position to exhibit the excitation or emission wavelength at that specific and selected wavelength (Lores et al., 1999, Martí nez-Galera et al., 2001, Subhani et al., 2013).
iii. Analytically photoinduced fluorescence derivatization is advantageous as it's not requisite the identification of target photoinduced fluorescent compound structure as long as its reproducible PIF signals are retrieved (Rocha et al., 2015).
iv. This PIF approach provides an advantageous analytical tool for rapid screening of non-fluorescent analytes in clinical, biochemical, pharmacological, and environmental studies (Durán-Merás et al., 2008, Rigas, 2012, López-Malo et al., 2017).
v. Despite, overwhelming advantages of post-column photochemical reaction detection, it's not completely free of limitations. For instance, the optimum mobile phase for clean chromatographic separation can affect the detection step. Similarly, eluent pH, solvent composition, presence of ion-paring reagents, buffers, nature of solvent, intensity and wavelength of light source, temperature, photoproducts stability and residence or reaction time could affect the overall sensitivity of this analytical technique (Fernández García-Borregón et al., 2000, Shen and Tomellini, 2007, Rocha et al., 2015).
vi. The fluorescence and PIF detection strategy are constrained to a confined group of analytes in particular that have only aromatic moiety (Fernández García-Bor regón et al., 2000, Fdil et al., 2003).
vii. Matrix effect (ME) is one of the serious drawbacks of the spectrophotometric approach which includes fluorescence detector. If sample extract is not treated appropriately then ME can doubtlessly enhance or suppress the signal intensity of target analytes and result in poor

repeatability, LOD and recoveries (Shen and Tomellini, 2007, Durán-Merás et al., 2008, Rocha et al., 2015, Muhammad et al., 2021).

viii. (xii) This technique is unable to identify the structure of targeted fluorescent-active photoproducts and unknown compounds, hence it merely relies on the retention times of their standard that can vary with small chromatographic influence (Lores et al., 1999, Fernández García -Borregón et al., 2000, Llorent-Martínez et al., 2011, Abdel-Salam et al., 2014, Farokhcheh and Alizadeh, 2014, Pulgarín et al., 2015, Rocha et al., 2015).

3. Applications of hyphenated LC-*hv*-FLD

LC-*hv*-FLD is a straightforward technique as it involves mere addition of a post-column photochemical reactor with conventional LC-FLD system as shown in Fig. 2 **(a).** Since its introduction, It is widely being for determination of analytes of different classes such as nitrosamines, pharmaceutical drugs, pesticides, vitamins and element as shown in Table S2 (Fedorowski and LaCourse, 2010, Marques et al., 2010, Debbab et al., 2012, Grant-Preece et al., 2017, Poole, 2017, Martín-Tornero et al., 2019).

LC separation of the analytes of same class and along with analytes of different classes is of great analytical interest for their accurate determination. However, separation of these analytes faces enormous challenges due to different functional groups and structural characteristics (Cappiello et al., 1994, González-Barreiro et al., 2003). Considering nature of target analytes and requirement of specific separation medium LC has been classified into popular reverse phase (RP), normal-phase (NP), size-exclusion (SEC), and ion exchange (IC) chromatography. RP-HPLC holds major share (≥90%) for the separation of analytes in environmental, pharmaceutical, life science, agricultural, food industry, medical, and biomedical fields. Due to versatility of HPLC the polar, non-polar, ionizable and ionic compounds separation are carried out conveniently by using simple buffered water and water-miscible organic modifier (MeOH or ACN) as mobile phase (Žuvela et al., 2019). NP chromatography is a valuable alternative to RPC for the separation of polar, weakly acidic or basic analytes because the stationary phase is relatively more polar to the mobile phase. (Jandera, 2011). Similarly, ion exchange chromatography is also a well-known separation mode for analysis of anions, cations, and charged organic compounds. This polymeric stationary phase rigidity, stability in wide pH range (0–14) compatibility facilitate the separation of polar and ionic organic compounds by offering the dual force of interactions including hydrophobic and electrostatic force of interaction (Muhammad et al., 2018a, 2018b, 2018c, 2019). Therefore, appropriate separation media for different classes of compounds were chosen by considering the analytes structural functional groups and characteristics. For instance, nitrosamines after photolysis turned into ionic form, which were efficiently separated on anion exchange column. Whereas, barbiturates, pharmaceutical drugs, pesticides and vitamins are mainly separated on reverse phase stationary phase considering their separation mechanism dominantly controlled by hydrophobic interactions. However, some of their acidic and basic group of analytes are also separated on ion exchange and normal phase stationary phase as detail of each class of compounds is give below and in **Table S2**.

3.1. Nitrosamines pollutant

N-Nitrosamines are carcinogens in nature and their presence in water have been of great concern as on disinfection various hazard byproducts such as ozonation, chlorination, and chloramination can come to being, that can react with nitrogen containing organic compounds in wastewater. Hence, it is pivotal to take *N*-nitrosamines into account when reclaim wastewater effluents through various filtration technique such as membrane nano-filtration (Lee et al., 2013, Li et al., 2016).

Fluorescence technique is less sensitive as compared to LC-MS/GC–MS, but effective detection of nitrosamines relies on the hemolytic cleavage of N-NO bond by UV irradiation, for subsequent reaction of formed nitric oxide, nitrite or amines with fluorescent labelling reagents. In 1976, Iwaoka and Tannenbaum *et al.,* first time used the photochemical reactor for the photolysis of nitrosamines for their subsequent determination by LC. The photochemical reactor was fabricated with capillary tubing of Pyrex glass offering residence time of serval minutes (Iwaoka and Tannebaum, 1976). The photolysis reaction generates NO^{2-}, which colorimetrically detected through Griess reaction. But generation of photoproduced nitrite (NO^{2-}) from nitrosamines in a sample depends and varies with photolysis conditions i.e., photo conversion of nitrite into nitrate can lead to uncertainty in accurate determination of nitrosamines. To evaluate these phenomenon, ion chromatography (IC) was utilized for the analysis of nitrosamine. It was investigated that *N*-nitrosodiethylamine facially decays on UV irradiation and undergoes heterolytic and hemolytic cleavage of N-N bond. It was observed NO^{3-} generated along with NO^{2-} upon UV irradiation of more than five min and its concentration continuously increased over 20 min of UV irradiation. Similar phenomenon has occurred during photolysis of nitrosamines and resulting NO^{-2} photoproduct subsequently oxidized into NO^{3-}. The optimum concentration of NO^{2-} was observed at pH 7. Hence, the conversion or oxidation of NO^{2-} into NO^{3-} is inevitable that caused error in previous determination as NO^{-3} cannot be determined by Griess reaction. Therefore, by using IC both of these photoproducts are separated on Dionex AS14 anion exchange column. Bases on their photo lability, a photolysis IC method appeared as a feasible and simple alternative for the sensitive estimation of nitrosamines (Li et al., 2016).

3.2. Pharmaceutical drugs

Nonsteroidal anti-inflammatory drugs (NSAID) are extensively administered in human and veterinary medicine for the cure of various illnesses such as osteoarthritis, rheumatoid arthritis, fever, severe chronic pain, post-trauma inflammation, muscular-skeletal disorders and as lipid regulator. The estimated yearly intake of these medicines was approximately to be more than $643 billion in 2006–2007. Most of these pharmaceutical compounds are continuously excreted in aquatic environment and causes potential hazards. Their concentration over 200 μg/mL causes serious toxic effects including acute renal cortex, gastrointestinal dysfunction, tonic-colonic seizure, apnea, papillae, and tubules (Bettaieb and Jean-

Jacques, 2001, González-Barreiro et al., 2003, López-Flores et al., 2007a, 2007b, Lozano and Escandar, 2013, Osório et al., 2013, Hurtado-Sánchez et al., 2015, Muhammad et al., 2019).

Therefore, HPLC-*hv*-FLD process was investigated to determine several neutral and acidic pharmaceutical active analytes including carbamazepine, zepam, ketoprofen, dihydrocarbamazepine, bezafibrate, naproxen, ibuprofen, acetylsalicylic and diclofenac in wastewaters. It was investigated the tolfenamic acid remained non-fluorescent even after UV irradiation, whereas ibuprofen and acetylsalicylic acid exhibited high PIF intensity with and without UV irradiation. Whereas, bezafibrate, dihydrocarbamazepine, diazepam, carbamazepine, ketoprofen, and diclofenac exhibitet strong PIF intensity after UV light irradiation, however naproxen strong intrinsic fluorescent intensity starts to decrease upon irradiation. Nature of solvent has significant impact on the PIF intensity of some drugs for instance diazepam, ketoprofen, and ketoprofen exhibited higher fluorescence intensity in MeOH as compared to ACN. But PTFE photoreactor life span is comparatively shorter in later solvent. Therefore, MeOH is chosen preferred solvent for their online PIF determination in river water samples. The PIF determination of acetylsalicylic acid appeared tricky, whereas, ibuprofen exhibited high LOD and tolfenamic acid remain non-fluorescent (González-Barreiro et al., 2003).

Clean extraction of polar or acidic drugs from complex biological samples is more difficult because of presence of ubiquitous impurities and matrix interferences. Therefore, an effective SPE-IC-*hv*-FLD method has been developed for the online cleaning of matrix interferences for their PIF determination in biological samples. A post-column photochemical reactor was integrated for the online conversion of non-fluorescent acidic pharmaceutical drugs (diclofenac, ketoprofen, bezafibrate, 2,4-dichlorobenzoic acid) into their respective fluorescent form. Three factors pH, solvent and irradiation time found to have significant influence on their PIF response. Basic pH is more conducive for their high PIF intensity considering the ease of hydrolysis and phtodegrdadtion stability in pH range of 7 to 11. Whereas, residence time of 20 s appeared long enough for maximum phototransformation of these drugs. The presence of organic solvents (ACN, MeOH, EtOH) in separation medium also have influence on their PIF intensity. There was no specific trend observed for these drugs, but diclofenac and ketoprofen exhibited high PIF response in ACN, while bezafibrate and 2,4-dichlorobenzoic acid displayed better PIF response in MeOH as compared to less polar organic solvent ACN. Generally, polar solvents i.e., alcohols assist to increase of PIF intensity of target analytes, but it's always not the case. Hence, solvent appeared to play pivotal role to reduce or prevent the triplet state excitation over singlet state excitation and result in poor fluorescence intensity and vice versa (Muhammad et al., 2019).

Sulphonamides are type of antibacterial that have been widely used in food-producing animals due to their ease of administration, high efficacy and low cost. Their concentration level in the blood in the range of 50–150 μg/mL are classified as therapeutically effective for majority of infections. As a result, the residues of veterinary drugs and their metabolites through application of animal wastes as fertilizers are contaminating soil and subsequently animal source foods. Therefore, it's indispensable for their trace determination in animal source food, soil and other sample matrices of concern is indispensable (Mahedero et al., 2002a, 2002b, Icardo et al., 2003, Mahedero García et al., 2005, Flores et al., 2007a, 2007b, Chen et al., 2009, Arroyo-Manzanares et al., 2015, Huertas-Pérez et al., 2016).

Concerning the complex nature of biological samples, an online SPE was coupled to HPLC-*hv*-FLD system for the extraction and determination of sulfadiazine, sulfapiridine, sulfamerazine, sulfa-methazine, sulfachloropiridazine, sulfamethoxazole, and sulfadoxine in serum samples. This online SPE was carried out on an anion exchange column with elution condition that were compatible with subsequent C-18 separation column. The SPE work on the basis of anion exchange mechanism in which sulfonamides retained on the pretreatment column and matrix interferences were discarded. Afterwards, the sample solvent was removed prior to sample injection for their separation on reverse phase column. These intrinsically non-fluorescent analytes passed through photochemical reactor prior to their detection at $\lambda_{ex}/\lambda_{em}$ = 240/350 nm wavelength as complete system diagram shown in Fig. 4 **(a & b)** (Arroyo-Manzanares et al., 2015). This study was further expanded for the determination of eight sulfonamide antibiotics in complex food samples (Huertas-Pérez et al., 2016).

Bisphosphonates are being administered for the treatment of patients having serious skeletal disorders such as Paget's disease, metastatic bone disease and osteoporosis. Therefore, to meet the growing demand, a reversed-phase ion-pair HPLC-PIF technique was utilized to determine multiple bisphosphonates including risedronic acid ibandronic acid, etidronic acid and alendronic acid in urine and dosage formulations. This method involves the oxidation of above bisphosphonic acids into orthophosphate by facile online peroxydisulfate assisted photolysis followed by the post-column reaction with molybdate to produce fluorescent active phosphomolybdate. The P–C bond of bisphosphonates is very facile to oxidize by UV irradiation. The presence of hydroxyl radicals generated from peroxydisulfate photolysis contributes to the high yield of these photochemical reactions. This phenomenon is conducive at the high concentration of peroxydisulfate (≥4.5 g/L) in strong basic or acidic media. However, when the concentration of peroxydisulfate is more than 8.0 g/L, oxygen and ozone generate due to its UV photolysis. But this phenomenon can be minimized to some extent by using the alkaline solution (pH 9) comprised of 19 g/L sodium tetraborate and 5.0 g/L potassium peroxydisulfate. Consequently, optimum photo-oxidation efficiency (70–100%) of these bisphosphonates was obtained. Similarly, residence time of about 14 s which controlled by length of photoreactor tubing and flow rate entailed optimum PIF peak response. At optimum condition, the resulting phosphate easily forms complex with molybdate to produce phosphomolybdate, which further reacts with thiamine to produce fluorescence active thiochrome (Pérez-Ruiz et al., 2009).

Methotrexate is an immunosuppressive and anti-inflammatory drug that has been applied to treat rheumatoid or psoriasis, lymphoblastic leukemia and other diseases. A HPLC-PIF-FD technique was established for the estimation of methotrexate and its metabolites 2, 4-diamino-N^{10}-methylpteroic acid and 7-hydroxymethotrexate in human plasma. These analytes along with 2, 4-diaminopteroic acid as an internal standard were isocratically separated and

sequentially online UV irradiated (245 nm) by passing through photochemical reactor for their detection at selected wavelength $\lambda_{ex}/\ \lambda_{em}$ = 368/452 nm. The mechanism of intrinsically non-fluorescent MTX phototransformation in the presence of hydrogen peroxide involves the formation of 2-amino-4 hydroxypteridine-6-carboxaldehyde along with 2-amino-4 - hydroxypteridine-6-carboxylic acid. It was investigated the presence of hydrogen peroxide slightly decreased the peak height but excitation/emission of phototransformed compounds remains unchanged. This confirms that UV irradiation at 245 nm is more effective as compared to 254 nm for the photo transformation of these compounds (Uchiyama et al., 2012).

About 1/3rd of the world adult population is exposed to tobacco smoke and leading to numerous preventable diseases including cancer that may ultimately lead to death. The absorbed nicotine in blood is primarily oxidize to cotinine and subsequently metabolized to rans-3′-hydroxycotinine, which after glucuronidation is extracted through the urine along with cotinine and nicotine. Therefore, monitoring of

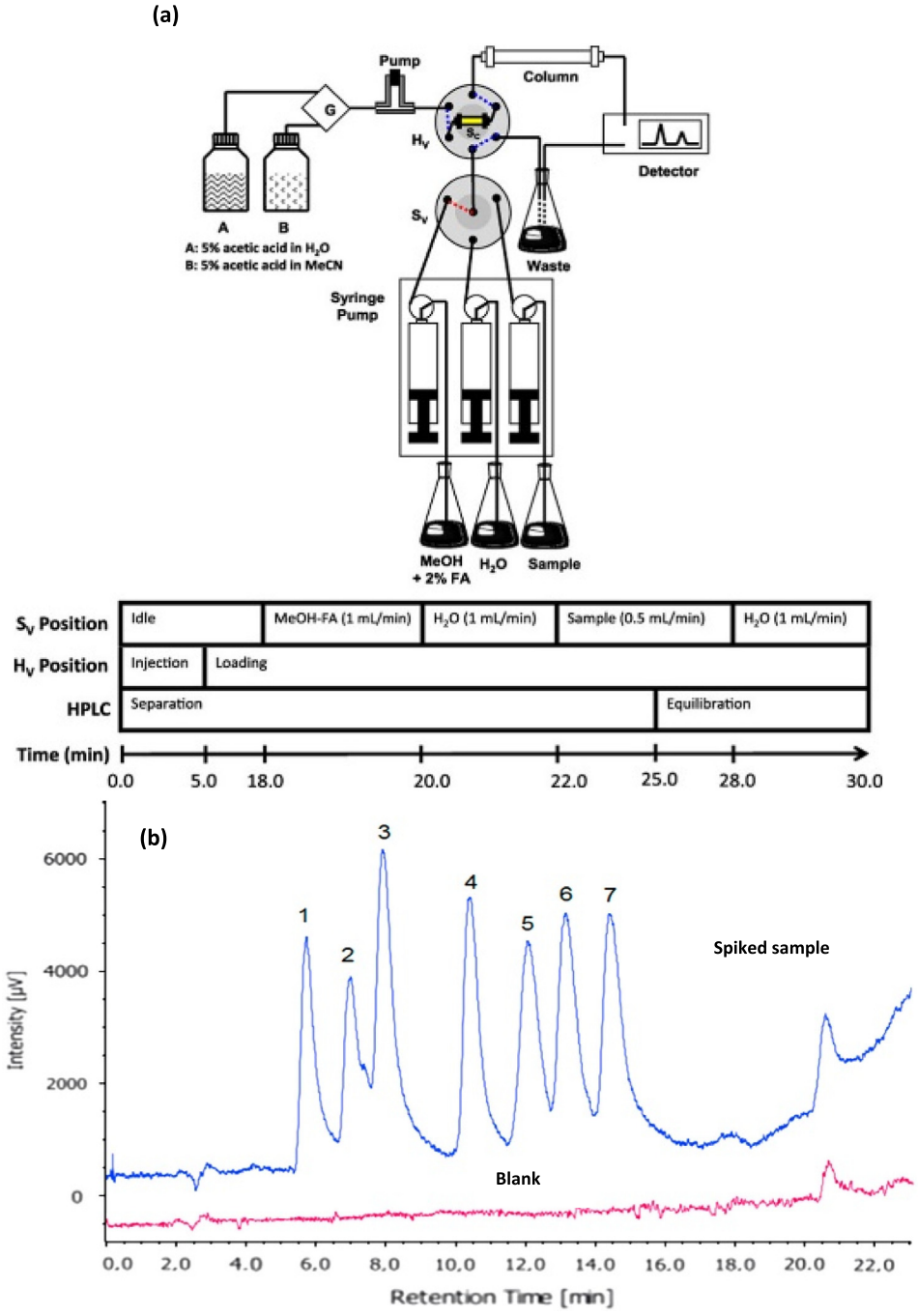

Fig. 4 (a) On-line SPE–LC-PIF-FLD setup; (b) On-line SPE–LC-PIF chromatogram of a blank and human serum sample spiked with seven sulfonamides at 30 mg/L, whereas i: sulfadiazine, ii: sulfapiridine, iii: sulfamerazine, iv: sulfa-methazine, v: sulfachloropiridazine, vi: sulfamethoxazole, vii: sulfadoxine. Reprinted from Arroyo-Manzanares et al., 2015 with the permission from Elsevier.

urine and serum nicotine is critical for the evaluation of subject (Yasuda et al., 2013, da Cunha et al., 2019). Hence, a simple method was designed to determine nicotine and cotinine in serum by means of HPLC-*hv*-FLD system. Both analytes along with 6-aminoquinoline as an internal standard were cleanly separated on RP column for subsequent online UV irradiation prior to their fluorescence detection. It was examined that nicotine and cotinine displayed optimum response in irradiation coil of length 9 m and 18 m, respectively. The irradiation coil of 18 m entailed maximum fluorescence response but it causes peaks broadening. Whereas, 9 m coil offered irradiation time of 26.5 s without peak broadening, but its PIF response was slightly lower than 18 m coil. Besides, pH of mobile phase played dual role not only in controlling the PIF response of analytes but also on their clean separation. It was investigated that reverse phase column at pH 4.5 is unable to separate three analytes and their PIF response continued to decreased as pH reduced to 3.5. Both analytes exhibited maximum PIF signals in mobile phase having 20% ACN content, but unable to retained on the column without addition of any ion-pairing reagent i.e. octanesulfonate. Hence, pH and solvent in mobile phase govern their separation along with influencing the photoirradiation efficiency and eventually fluorescence intensity (Yasuda et al., 2013).

Varenicline is structurally similar to nicotine, and being used to ease symptoms due to nicotine-addiction. A HPLC-*hv*-FLD method was developed for the estimation of varenicline in urine by utilizing HPLC-*hv*-FLD as shown in Fig. 5 **(a).** The variation of the content MeOH content in mobile phase govern the separation and symmetry of peak. If the MeOH proportion is lower in mobile phase, the varenicline peak becomes unsymmetrical. However, with the increase of its proportion to 70%, the retention time of analyte decreased and peak symmetry increased. Whereas, varenicline displayed maximum PIF response in strongly alkaline medium after 8 min of UV irradiation. This elongated irradiation time causes the peak broadening. On contrary, the generated photoproduct is stable up to 5 min to 90 min without tarnishing its fluorescence response. It reflects the possibility of using indirect determination of target analytes in batch analysis. It was investigated that the chromophore of varenicline is not affected after UV irradiation because the increase of its PIF response occurs without significant change in fluorescence excitation/emission maxima. This high fluorescence quantum yield is correlated with formation of rigid and stable structure having cycle and bridge formed after breaking of 7-member cycle group that was prohibiting the delocalization of electrons. This photolysis break the C-N bonds entailed the 5–carbon group having planer conjugated unsaturated bonds to the aromaticity of the molecule as detailed mechanism is given in Fig. 5 **(b & c)** (da Cunha et al., 2019).

3.3. Pesticide analysis

The usage of pesticide in modern agricultural methods has increased considerably since 1975. According to United Nations estimates less than 1% of used pesticides reached crops. As result the remaining pesticides end up contaminating ecosystem compartments especially soil, ground and surface water and their persistence is matter of extreme concern due to their potential carcinogenicity and various levels of toxicity (Malato et al., 2001, Liu et al., 2007, Medina et al., 2009, Mbaye et al., 2015, Nie et al., 2016, Bakhoum et al., 2020a, 2020b, Toloza et al., 2020, Intisar et al., 2022). To keep track of the ever-increasing usage of pesticides and their environmental pollution, LC-*hv*-FLD emerged as a low-cost analytical approach for residue analysis of any contaminants, including pesticides. (Poole, 2017, Toloza et al., 2020).

Carbendazim is a widely used fungicide for killing a broad range of fungi causing harm to vegetables, nuts, turf, fruits, and field crops (Panadés et al., 2000, Mazellier et al., 2002). Similarly, herbicides occupied about 50% share of agricultural pesticides, among these phenylurea (BUs) derivatives are emerging herbicides to control a large number of broadleaves weeds and annual grasses in a number of crops. The public health concern has increased due to their residue's persistence in food products and environment. Therefore, the European Union regulated and permitted 0.05 mg/kg of any single herbicide in agricultural food, whereas, UK and European countries allow 0.5 μg/L of total pesticides and 0.1 μg/L of single pesticide in drinking water (Gil-Garcia et al., 2001, Martínez-Galera et al., 2001, Muñoz de la Peña et al., 2002, de la Peña et al., 2003, Irace-Guigand et al., 2005, Gil García et al., 2006, Gil García et al., 2007, Mughari et al., 2007, Galera et al., 2008, Piccirilli et al., 2008, Catal et al., 2011, Llorent-Martínez et al., 2011, Diaw et al., 2013, Arancibia and Escandar, 2014, Diaw et al., 2014, Farokhcheh and Alizadeh, 2014, Thiaré et al., 2015, Lozano and Escandar, 2016, Bakhoum et al., 2019a, 2019b, Diaw et al., 2019, Bakhoum et al., 2020a, 2020b).

Therefore, HPLC-*hv*-FLD technique was used for strict monitoring and assessment of human exposure to various insecticides (diflubenzuron, lufenuron, triflumuron, hexaflumuron, and flufenoxuron) residues in tomato samples. The hydrophobic interaction between analytes and stationary phase of reverse phase column were exploited for their clean separation with the use of water and methanol as mobile phase. The methanol as an organic solvent in separation eluent appeared more conducive for their maximum PIF response as compared to ACN. Whereas, analytes irradiation time was managed by variation of flow rate. When the flow rate was decreased, all analytes fluorescent response increased respectively, except flufenoxuron. In order to determine all the analytes at the same time, the comprised irradiation time was chosen to avoid the band broadening. But this irradiation time prohibit to obtain lowest possible LOD of other four analytes except flufenoxuron. The pH of separation medium doesn't have any significant influence on the fluorescence response. This method appeared selective for their determination in the presence of 30 other commonly used interfering pesticides, except thiabendazole, which interferes when its concentration is higher than 30 ng/mL. LOD (0.5–2.1 μg/kg) appeared better to HPLC–DAD, and in some case comparable to HPLC–MS. (Martínez-Galera et al., 2001).

Apart from these, propanil is anilide herbicide is highly water soluble and toxic, which in combination with other effective herbicides is being used to protect the paddy fields. Therefore, determination of propanil along with phenylureas (diuron, linuron, isoproturon, and neburon) was carried out by using HPLC-*hv*-FLD in river water samples. Analytes PIF intensity was strongest in aqueous mobile phase having MeOH as an organic modifier as compared to ACN. Under optimized conditions, the developed method show excellent

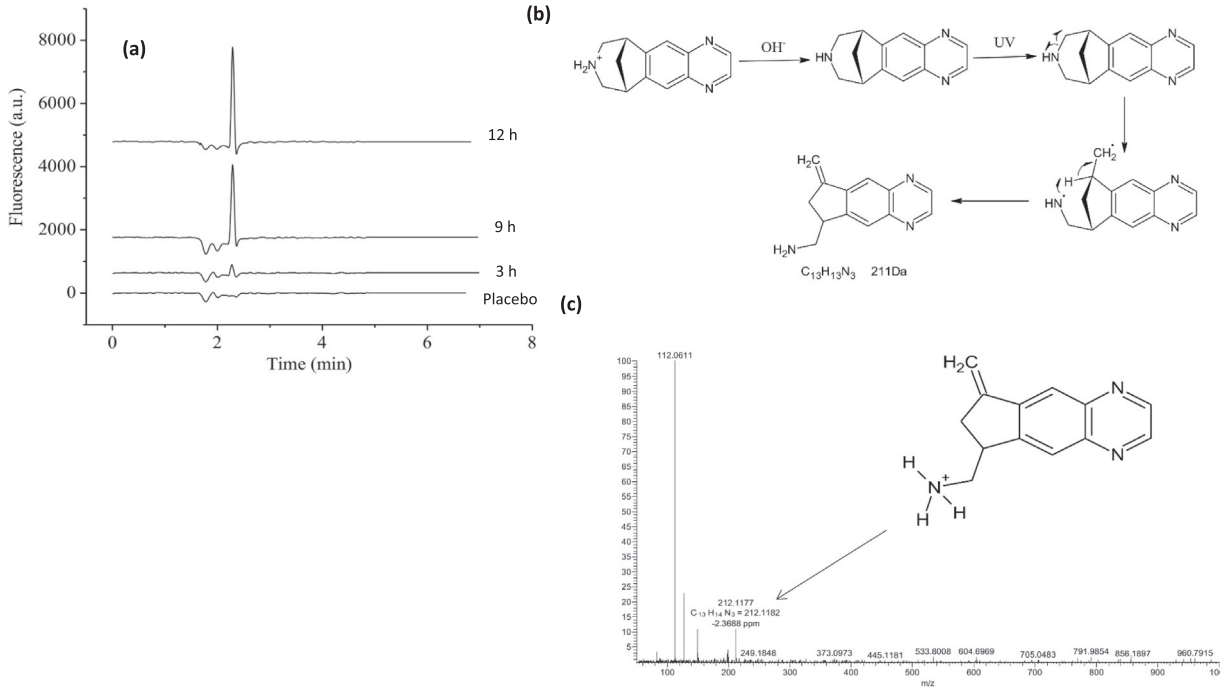

Fig. 5 PIF (a) chromatograms of varenicline in urine at four intervals placebo, 3 h, 9 h and 12 h administration of the drug; (b) proposed reaction scheme for the photo-derivatization of varenicline,and (c) Mass spectrum of photoproduct of varenicline in basic 0.1 mol/L NaOH medium. Reprinted from (da Cunha et al., 2019) with the permission from Elsevier.

sensitivity by using only light as derivatizing reagent (de la Peña et al., 2003, Mughari et al., 2007, Zhou et al., 2013). Apart from UV irradiation, effect of different complexing agent such as *β*-cyclodextrin (*β*-CD) and hydroxypropyl- *β*-cyclodextrin (HP-*β*-CD) and reaction media pH upon the PIF intensity of four phenylurea herbicides (isoproturon, neburon, diuron and linuron,) was investigated. It was observed both cyclodextrin media have increased all analytes PIF wavelengths from $\lambda_{ex}/\ \lambda_{em}$ = 302/356 nm to $\lambda_{ex}/\ \lambda_{em}$ = 321/437. This significant red-shift in the range of 8 to 67 nm (except linuron) can be attributed to the creation of inclusion complexes between analytes photoproducts and cyclodextrin. Their PIF emission intensities of analytes continue to increase with gradual increase of complexing agent (cyclodextrin) concentration and reached a plateau value at their concentration of 1.02×10^{-2} M. In drawback, the irradiation time was appeared much longer in the presence of complexing agent than in ultrapure water. This exhibited the complex formation has slow down the photolysis reaction, as result the PIF signals of analytes continue to increase even after 65 min of UV irradiation. It indicates that online UV irradiation is not suitable to obtain the maximum PIF intensity of these analytes in the presence of complexing agent (Mahedero et al., 2002a, 2002b).

Analysis of BUs pesticides from complex samples such as vegetables is challenging due to ubiquitous presence of polar and non-polar interferences. To meet these challenges, the multidimensional LC demonstrated to be a promising method for discarding the matrix interferences from the sample with ease and automation. Besides, coupling of different columns having different separation mechanism is also an attractive substitute for the selective estimation of a set of analytes. LC-LC-*hv*-FD technique has been utilized for the determination of five insecticides of benzoylurea group, including triflumuron, flufenoxuron, diflubenzuron, lufenuron and hexaflumuron from four complex vegetables (aubergine, cucumber, green bean, tomato) dichloromethane extract. The separation power of first reverse phase column allows the efficient and early clean-up of matrix interferences. Afterwards, the second-dimension column was able to simultaneously separate all these five analytes for their subsequent PIF determination at levels below established MRLs. In addition, methanol as an organic solvent and eluent flow rate of 0.5 mL/min offered optimum PIF response and clean separation of the selected analytes (Gil García et al., 2004).

To diminish the effect of matrix interferences, an online enrichment of five BUs insecticides including lufenuron, flufenoxuron, diflubenzuron, triflumuron and hexaflumuron, from ground water samples was carried out by using a short reverse phase column. The strong hydrophobic force of attraction between benzoylureas insecticides and pre-treatment column allows the enrichment of sample volume up to 50 mL, while eliminating the redundant amount of polar matrix interferences into waste. Afterwards, all analytes were baseline separated on second dimension reverse column by using a mobile having eluotropic strength higher than aqueous sample prior to their online PIF detection at $\lambda_{ex}/\lambda_{em}$ = 344/418 nm. This designed system successfully has overcame the challenges of sensitivity, co-extraction, and matrix interference i.e., polar humic acid, but non-polar matrix interference species problems still remain unresolved. The use of 30% MeOH as an organic

modifier not only enhanced enrichment efficiency but also significantly enhanced the PIF intensity of analytes (Gil García et al., 2006).

Chronologically, pyrethroids after organochlorines, organophosphates, and carbamates constitute the fourth biggest share of insecticides. The growing application of pyrethroids is causing serious risk of infertility, nerve disorders, breast cancer, immune system degradation, and respiratory, immunological and cardiovascular diseases. (López-López et al., 2001, Martínez Galera et al., 2005, Wen et al., 2005, Galera et al., 2006, Vázquez et al., 2008, Bagheri et al., 2009, Mbaye et al., 2009, Mbaye et al., 2011, Ruiz-Medina et al., 2019, Diouf et al., 2020). Therefore, HPLC-*hv*-FLD method was developed for the simultaneous multi-residue analysis of seven pyrethroids insecticides in complex vegetable matrices. It was observed pH didn't impart any significant change on analytes PIF intensity, but matrix effect was observed for all pyrethroids except cyfluthrin, deltamethrin, and bifenthrin during their determination in matrix-matched and solvent-based standards. The poor PIF signals intensity was attributed due to poor or incomplete photoderivatization of selected pyrethroids or fluorescence quenching caused by sample co-extracts. This problem to some extent was overcome by preparing and analyzing matrix-matched standard for their quantification. The developed method LOQ (0.8 – 9.0 µg/kg) were significantly better than TLC and GC-ECD technique, and minor than the MRLs set by European Union countries (López-López et al., 2001, Martínez Galera et al., 2005, Wen et al., 2005, Galera et al., 2006).

Coating fiber 3-(trimethoxysilyl) propyl amine for solid phase microextraction (SPME) was synthesized for efficient extraction of pyrethroids (cyfluthrin, cypermethrin, and flumethrin) from environmental sample (water) prior to determination of extracted analytes by using HPLC-PIF-FLD technique. A homemade post-column photochemical was designed for the online photochemical derivatization of these intrinsically non-fluorescent impurities for their determination at wavelength at $\lambda_{ex}/\lambda_{em}$ = 283/330 nm. It was investigated all these pyrethroids exhibited excitation/emission maxima in proximity of each other. The elongated irradiation time was found to have positive impact on the PIF intensity of these analytes. Therefore, flow rate of 1.5 mL/min was applied to obtain appropriate chromatographic separation and PIF response as shown in Fig. 6 **(a)**. Interestingly, cypermethrin pyrethroid displayed two peaks under optimized PIF condition which is indication of its *cis* and *trans* isomers. The photoproducts of cyfluthrin, cypermethrin, and flumethrin were confirmed by GC–MS and it was suggested that the cleavage of esteric bond entailed fluorescent active product as shown in Fig. 6 **(b)** (Vázquez et al., 2008, Bagheri et al., 2009).

A HPLC-FLD technique was established to estimate non-fluorescent kresoxim-methyl by offline photochemical derivatization in water and grapes samples. The target single analyte was extracted by DLLME procedure and transferred in 20 mL tubes (quartz) and placed into a photochemical reactor (6 W mercury lamp inside 200 mm polyvinyl chloride cylindrical box) for about 45 s UV irradiation. The photo irradiated sample solution was injected to the pre-running chromatographic system for the separation and detection of tebuconazole and kresoxim-methyl photoderivative at $\lambda_{ex}/\lambda_{em}$ = 226/325 nm and $\lambda_{ex}/\lambda_{em}$ = 370/430 nm, respectively as shown in Fig. 7**(a).** The UV photo derivatization of 1.0×10^{-6} mol/L kresoxim-methyl imparts significant molecular structure changes for its conversion into fluorescent form. Its strong PIF intensity can be illustrated by formation of fluorescent active photo-product because of greater structural rigidity as compared to original non-fluorescent kresoxim-methyl as shown on proposed mechanism given in Fig. 7**(b).** In case of kresoxim-methyl, the UV irradiation cause photolysis of the C–O bond occurs that connect the two aromatic rings, while the aromatic rings bond remains intact. This photolysis led to cyclization with two rings via carbonyl group, enhancing rigidity, conjugation of double bond system and eventually electron delocalization. This characterization of formed photo-product was carried out by LC-MS analysis of UV irradiated solution of kresoximmethyl. Obtained mass spectrum given in Fig. 7**(c)** depicts that the appearance of peak at *m*/*z* 176 Da is the confirmation of proposed photo-product formed after the removal of a hydrogen (M−1) (Toloza et al., 2020).

Chlornicotinyl insecticides such as imidacloprid (IMI) are utilized against chewing and sucking pests, that causes the depletion of honeybee. The continuous increasing application of pesticides has entailed undeniable impacts in the natural water quality, and overall environment (Vílchez et al., 2001, Martínez Vidal et al., 2002, Rancan et al., 2006, García et al., 2007, López Flores et al., 2007, Subhani et al., 2013, Fuentes et al., 2015, Jiménez-López et al., 2016a, 2016b, Jeria et al., 2017, Jiménez-López et al., 2018, Muhammad et al., 2018a, 2018b, 2018c, Jiménez-López et al., 2019a, 2019b, Subhani et al., 2020).

Therefore, an environment-friendly methodology proposed by using a short column switching liquid chromatography technique hyphenated with post-column photochemical derivatization system for the fluorescence determination of IMI and its main metabolite 6-chloronicotinic acid from honeybees samples. The designed column switching system have eliminated the most of the interfering compounds from the honeybee sample extract. The online clean-up step made possible the clean separation of target components on reverse phase column by using simple eluent (acetonitrile: water) in gradient mode. It was observed intrinsically non-fluorescent IMI aqueous solutions on UV irradiation produce PIF signal of high intensity. On isolation and identification 1-(6-chloro-3-pyridylmethyl)-2 -(hydroxyimino)-3, 4-didehydroimidalozolidene appeared as a potential photodegradation product, which show fluorescence signal at wavelengths $\lambda_{ex}/\lambda_{em}$ = 334/377 nm. Its relative PIF intensity reached its peak in aqueous media having pH in the range of 11.5 to 12.2. Whereas, the PIF intensity doesn't change much on variation of temperature from 5 to 18 °C, but it started to diminish on further increase of temperature from 20 to 70 ℃. Therefore, temperature around 5.0 ± 0.5 ℃ is suitable for its determination (Vílchez et al., 2001, García et al., 2007).

García et al., investigate the phenomenon of high PIF intensity for IMI in basic media (pH ~12) by adding an extra post-column pump and mixing tea to protect the silica based columns (García et al., 2007). To simplify the system while having optimum PIF intensity of target analytes, Subhani *et al.,* designed a new hyphenated IC-*hv*-FD technique for the simultaneous determination of two intrinsically non-fluorescent analytes from two different classes namely IMI and carbendazim in water samples**.** Both analytes were isocratically separated on IonPacs AS11 column by pumping 40 mM KOH having minuscule content ACN 10% (v/v). The sepa-

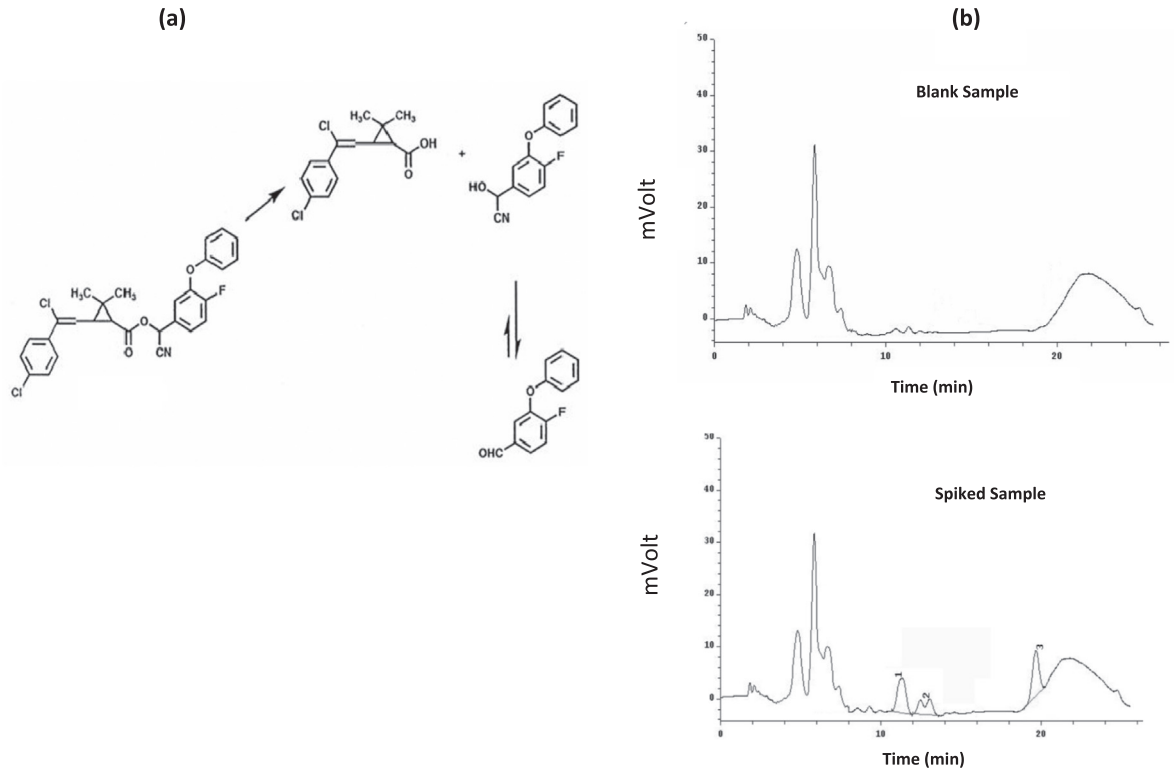

Fig. 6 (a) Photo irradiated obtained fluorescent active product of flumethrine; (b) A SPME-HPLC-PIF-FD chromatogram retrieved by analysis of Jajroud river water samples an blank sample and spiked sample with (1) cyfluthrin, (2) cypermethrin, and (3) flumethrin. pyrethroids at 10 µg/L under optimized conditions. Reprinted from (Bagheri et al., 2009) with the permission from Wiley.

rated analytes were passed through homemade photochemical reactor for their online UV irradiation and subsequent detection at selected wavelengths $\lambda_{ex}/\lambda_{em}$ = 332 nm/367 nm (IMI) and $\lambda_{ex}/\lambda_{em}$ = 247 nm/470 nm (carbendazim). The developed method displayed satisfactory analytical figures of merit in all three water samples (groundwater, lake water and river water) (Subhani et al., 2013). The same system with minor modification in column and eluent was further applied on other neonicotinoids such as thiacloprid (Subhani et al., 2014), nitenpyram and 6-chloronicotinic (Muhammad et al., 2018a, 2018b, 2018c), IMI and clothianidin (Muhammad et al., 2018a, 2018b, 2018c) acetamiprid and 6-chloronicotinic acid (Subhani et al., 2020).

Plant growth regulators such as gibberellic acids are extremely important group of synthetic pesticides that have physiological activity characteristics similar to their respective plant hormones (natural pesticides) to effectively inhibit, modify or promote, plants development and growth. (Murillo Pulgarín et al., 2013, Murillo Pulgarín et al., 2014). Humans are exposed to through diet and show acute dermal toxicity at LD50 > 2 g/kg, acute inhalation-negative LC50 at 2.98 mg/L & LC50 > 5.9 mg/L and overall toxicity category is classified as III. Therefore, its MRL of 0.15 mg/L value has been established in various grapes, citrus fruits, leafy vegetables, blueberries, and stone fruits (Murillo Pulgarín et al., 2013). José A. Murillo *et al.,* established a simple scheme to determine these in various complex samples (technical formulation, tomato, orange, strawberry tree berry) by using LC-PIF-FLD system as shown in Fig. 8**(a)**. The photochemical system allows the 6 min of UV (at 253.7 nm) irradiation in a solution composed of 50% (v/v) methanol and buffer having pH 5. The photochemical dimerization and photoaromatization with elimination of carbon dioxide resulted in various fluorescent photoproducts as shown in Fig. 8 **(b).** The fluorescent intensity of these formed photoproducts is affected by the various factors. Solvent is vital parameter considering the insolubility of gibberellic acid in water. The presence of alcohol EtOH/MeOH up to 5% along with irradiation time of 3.3 min remarkably enhanced its PIF intensity. This phenomenon can be attributed to the formation of strong oxidant hydroxyl radical (·OH) that led to high fluorescence response. The polarity of solvent appeared to have no effect on excitation/emission spectrum. The irradiation time of 6 min was found optimum. The shorter or longer time than this entailed lower PIF response because former time have lower conversion rate into fluorescent products, while later led to degradation of formed photoproducts. The influence of pH in the range of 1.0–12 on PIF intensity of gibberellic acid was investigated by adding different volume of NaOH/HCl in its solution prior to irradiation. It reflected that gibberellic acid fluorescent intensity remained constant from pH 4–7, hence pH 5 was chosen to have optimum PIF intensity. Whereas, temperature has great theoretical and practical significance on PIF intensity of analytes by enhancing their molecular thermal motion. Herein, the high temperature increased the chance of radiation less transition, and subsequently poor PIF quantum yield was observed. Therefore, 20 °C was chosen for optimum PIF intensity of gibberellic acid. (Murillo Pulgarín et al., 2013).

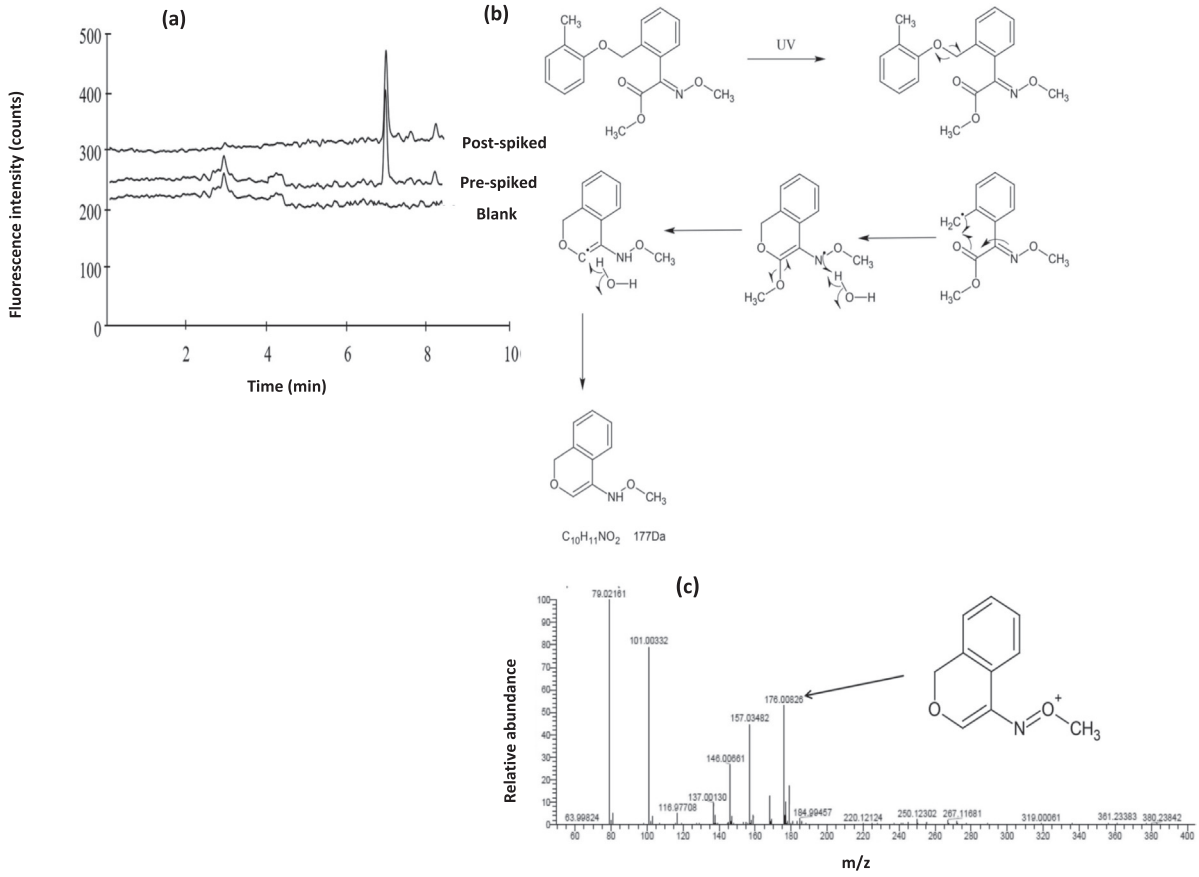

Fig. 7 **(a)** Chromatograms of purple grape samples extracts; **(b)** proposed mechanism of ultraviolet irradiation photo-derivatization of kresoxim-methyl; **(c)** Mass spectrum of photo-derivatized 1.0×10^{-6} mol/L kresoxim-methyl. Reprinted from (Toloza et al., 2020) with permission from Taylor & Francis.

Chlorophenoxyacid herbicides kill plants selectively or non-selectively but their intensive use through a systematic cycles is contaminating the food chain, water reservoirs, and biological systems (García-Campaña et al., 2001, Almansa Lopez et al., 2003, Fdil et al., 2003, Arancibia and Escandar, 2014, Pulgarín et al., 2015). Their low or non-fluorescent behavior is attributed to the presence of heavy atom such as chlorine that significantly increase the excited singlet to triplet state intersystem crossing rate constant. However, the presence of aromatic ring has made their PIF determination possible (-García-Campaña et al., 2001, Fdil et al., 2003). This concept has led to photochemical derivatization based determination of chlorophenoxyacid herbicides including 2-(2-methyl-4-chorophenoxy) propionic acid (MCPP), 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2, 4, 5-trichlorophenoxyacetic acid (2,4,5-T), and 2,4-dichlorophenoxyacetic acid (2,4-D). Micellar media have appeared effective for enhancing their PIF intensity. Henceforth, this methodology was named micellar-enhanced photoinduced-fluorescence (MEPIF) because the PIF intensity was significantly enhanced by the media while reducing the content of organic solvent. Therefore, a MEPIF was designed for the simultaneous estimation of these herbicides including MCPP, MCPA, 2, 4, 5-T, 2, 4-D. Effect of various non-ionic (Triton X-100), anionic (SDS) and cationic (CPC, CTAC) surfactants on their PIF intensity was investigated and CTAC appeared as significant PIF intensity. Besides, various critical variables and parameters including UV irradiation time and surfactant concentration have been sequentially optimized by Sequential Response Surface Methodology (SRSM) with the application of Doehlert designs to get their optimum PIF intensity. The developed method appeared effective with excellent spiked recoveries of all these herbicides at selected fluorescence wavelengths $\lambda_{ex}/\ \lambda_{em}$ = 270/298 nm (Almansa Lopez et al., 2003).

3.4. Mycotoxins analysis

Mycotoxins have two main types of aflatoxins (AFs) and ochratoxin A (OTA). Aflatoxins G1, G2, B1 and B2, and secondary metabolites of *Aspergillus parasiticus* and *Aspergillus flavus*, are also a group of analytes that are similar in structure to mycotoxins that are causing chronic and acute toxicity such as carcinogenic, mutagenic, teratogenic effects in various organisms and immunosuppressive effect are posing serious effect to animal and human wellbeing. These are widely found in variety of foodstuff, medicinal plants and spices. Due to rising concern, International Agency for Research on Cancer (IARC) categorized these aflatoxins as group 1 of human carcinogens, whereas, a maximum level has been set by European Union (EU) i.e., 2 μg/kg for AFB1 and 4 μg/kg for total afla-

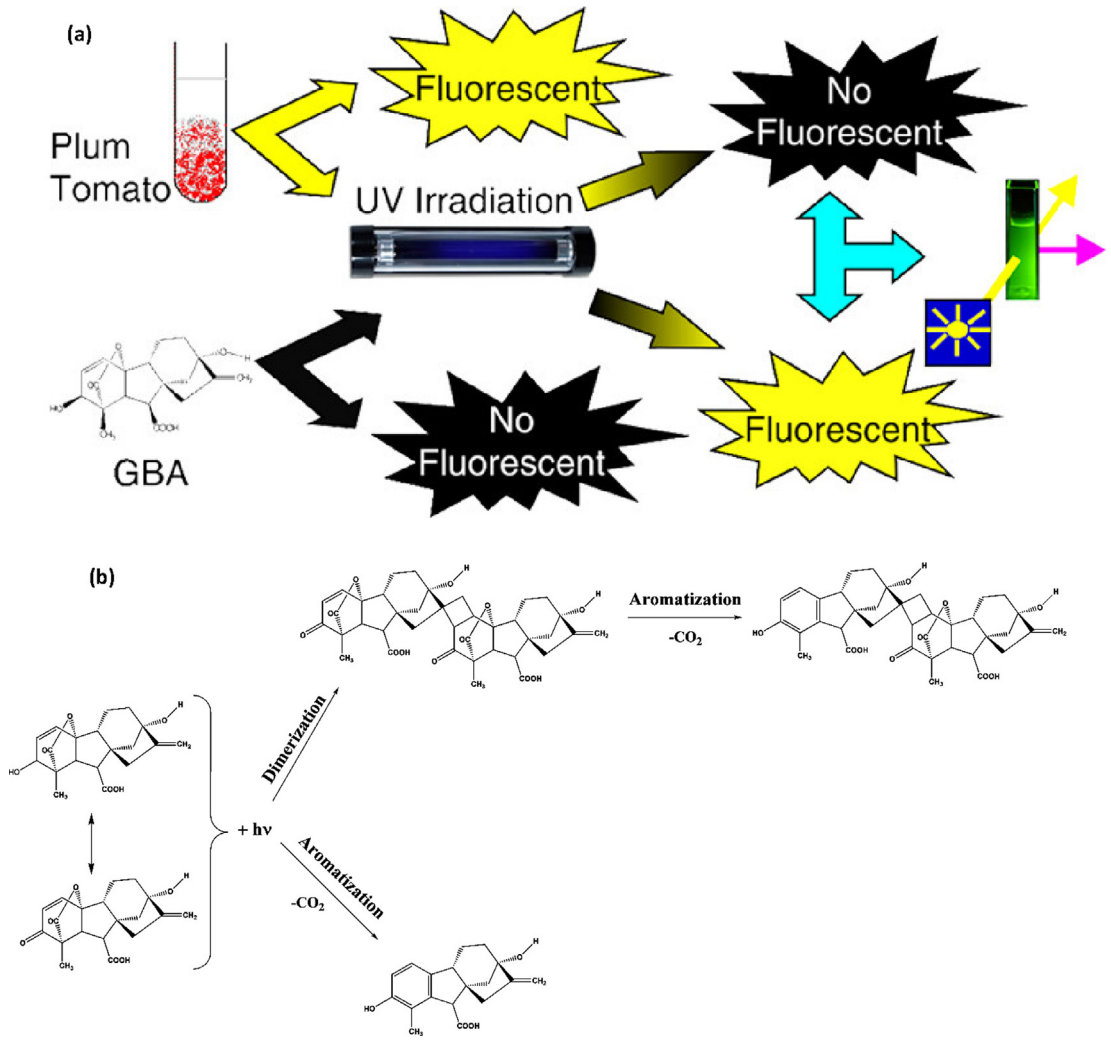

Fig. 8 (a) Systematic diagram of PIF phenomenon; (b) mechanism for the photochemical reactions of gibberellic acid. Reprinted from (Murillo Pulgarín et al., 2013) with permission from American Chemical Society.

toxins in cereals, dry fruits, and nuts that are directly consumed by human being (Regulation (EC) No. 1881/2006.) (Waltking and Wilson, 2006, Muscarella et al., 2009, Kong et al., 2013, Rahmani et al., 2013, Pavšič-Vrtač et al., 2014, Liu et al., 2016, Hamed et al., 2017, Shuib et al., 2017, Huertas-Pérez et al., 2018, Bao et al., 2019, Yu et al., 2019a, Yu et al., 2019b, Muñoz-Solano and González-Peñas, 2020, Zhang et al., 2020).

Therefore, Joshua et al., introduced a LC technique for the clean separation of six aflatoxins (B1, B2, G1, G2, M1, and M2), along with zearalenone and ochratoxinaon in a single analytical run and their post-column photochemical derivatization fluorescence detection (Waltking and Wilson, 2006, Muscarella et al., 2009, Pavšič-Vrtač et al., 2014). A.E. Waltking *et al.,* compared the LC hyphenate with post-column PIF derivatization method to officially considered iodine and Kobra cell derivatization systems. There wasn't any significant difference found between the techniques for their determination in peanuts, but photo derivatization method gave much higher recoveries for the aflatoxins B1 and B2 than the Kobra cell method (Waltking and Wilson, 2006, Muscarella et al., 2009).

Another collaborative study involving fifteen laboratories from six different countries used the immuno-affinity column cleanup and LC-PIF-FLD system to establish the repeatability, reproducibility and accuracy characteristics for the estimation of aflatoxins (B1, B2, G1, and G2) in various food items (peanut oil, olive oil, sesame oil). The established technique exhibited excellent recoveries in the range of 76–97% with RSDs in the range of 3.4–14.9%, whereas between-laboratory reproducibility ranged 6.1–18.1% (Bao et al., 2019).

The simultaneous sensitive and selective determination of multiple mycotoxins from complex sample matrices is of huge interest. Considering the pressing need, an ultrasound-assisted solid–liquid extraction and immunoaffinity column clean-up based HPLC-PIF-FLD method was developed for the simultaneous determination of multi-mycotoxin aflatoxins B1, B2, G1, G2 and ochratoxin A (OTA) in thirteen edible and medicinal nutmeg samples. For sensitive determination of target analytes, various parameters of HPLC-PIF-FLD system such as column temperature, mobile phase, elution procedure, excitation and emission wavelengths were optimized. The FLD detection was performed at $\lambda_{ex}/\ \lambda_{em}$ = 360/440 and $\lambda_{ex}/$

λ_{em} = 333/460 nm for AFs, and OTA, respectively after photoreactor UV irradiation at 254 nm. The results of this developed method showed that four nutmeg samples were contaminated with AFs and OTA (Kong et al., 2013).

Phosphorus is a vital nutrient consumed by most of the organisms for basic process of life. The continuous use of phosphorus containing fertilizers and chemicals are increasing its concentration in different compartment of ecosystem. Consequently, the gradual exposure to organophosphorus pesticides causing acetylcholine accumulation that can interfere with muscular response and results in probable death (Gómez-Benito et al., 2013). In line of this, a post-column reaction-based detection of organophosphorus pesticides (phosphate, acephate and methamidophos) was performed by photolysis of organophosphorus pesticides by *UV* irradiation in presence of peroxydisulfate. Resulting orthophosphate was treated with molybdate to form a reactive molybdophosphoric acid, that instantaneously reacted with thiamine to form fluorescent active thiochrome. This fluorescent product of organophosphorus pesticide was detected at λ_{ex}/ λ_{em} = 375/440 nm. The high PIF intensity of these analytes is due to presence of hydroxyl radical generated by photolysis of peroxydisulfate. Effect of peroxydisulfate concentration and mobile phase pH on photo irradiation-based conversion of analytes (acephate, methamidophos) into orthophosphate form was investigated. At optimum condition the efficiency of the formation of orthophosphate was close to 100 % and its peak response is close to equivalent amount of orthophosphate at identical conditions. The pH of peroxydisulfate was adjusted to 9.2 in order to minimize the photoxidation of orthophosphate into CO_2 bubbles. Besides, the irradiation time of 22 s was chosen by varying the coil length, and total flow rate to obtain the maximum fluorescence intensity of target analytes. All three organophosphorus pesticides were isocratically separated on ODS column by using water-acetonitrile mobile phase. Developed method showed excellent analytical figures of merits with intra- and inter-day precision values less than 1.2% and 2.1 %, respectively (Pérez-Ruiz et al., 2005).

3.5. Vitamins

Thiamine also known as vitamin B1 is commonly found in small amount in all foodstuffs, but carbohydrate enriched foods such as, cereal products, cereal grains, meat, vegetables, milk and meat are their good source (Viñas et al., 2003, Gatti et al., 2004, López-Flores et al., 2005, ShengLin et al., 2013). A HPLC-PIF-FLD method was developed to determine the folates level in impotent biological and food plants. It was investigated that 6-formilpterin and p-aminobenzoyl-L-glutamic acid are the main folic acid photoproducts that are responsible for the fluorescent signal of this intrinsically non-fluorescent FA. Therefore, E. M. Tornero *et al.,* conducted a compressive study for the identification of these photoproducts, along with the evaluation of various factors such as nature of the irradiation lamp and irradiation time on overall PIF intensity. It was observed that FA turn into fluorescent active specie on UV irradiation, while the 6-formilpterin and p-aminobenzoyl-L-glutamic acid are intrinsically fluorescent active but on irradiation their PIF intensity remarkably enhanced. The PIF intensity of FA has been attributed to the formation of fluorescent active 6-formylpterin, that's rapidly turn into pterin-6-carboxylic acid and finally into pterin**.** This phenomenon was verified by characterization of photoproducts by HPLC-MS **Figure S2 (A - C).**The HPLC-PIF-FLD method was developed to analyze FA, tetrahydrofolic (THF) and 5-methyltetrahydrofolic acids (MTHF) in biological and food samples Fig. 9.The separation of all analytes from extract was achieved on reverse phase column. A post-column photo reactor made up of a PTFE tube winded around 10 W xenon lamp was used for the online UV irradiation to enhance their PIF intensity for the sensitive determination by fluorescent detector at λ_{ex} / λ_{ex} = 280/360 nm and 280/440 nm. Moreover, effect of irradiation time, and presence of N_2, and H_2O_2 in separation medium on PIF signal were also investigated prior to their determination in cereals, tomato and spinach samples (Martín Tornero et al., 2017).

3.6. Elements

Selenium is a critical element in ecosystem due to its roles as toxic substance at high concentration and essential nutrient at low concentration. Selenide, selenocystine, selenomethionine and related organoselenium or inorganic selenite compounds are very effective in preventing some chronic disease such as cancer and heart disease. Therefore, a high-performance anion-exchange chromatography–atomic fluorescence spectrometric technique (HPLC-AFS) was established for the separation of selenite, selenocystine, selenomethylcysteine, and selenomethionine on an anion-exchange AminoPac PA10 column. The polar analytes having high pK_a tend to retain weekly on column and elute prior to low polarity analytes having low pKa values. For example, selenourea, selenocystine, and selenomehionine are eluted successively using NaOH as a mobile phase. The two carboxyl groups on selenocystine molecular structure are facilely ionized that strongly hold it on the column. Its anion exchange elution can be carried out only by using a high strength eluent i.e., sodium acetate (NaAc) solution. Similarly, selenite high acidity due to pK_a value of 6.60 is the main reason for its strong retention on AminoPac PA10 column. This could be eluted by gradient acetate eluent. After the clean elution of selenourea, selenomethionine and selenomethylcysteine, an additive NaAc was incorporated into eluent for the elution of selenite and selenocystine. But these separations are only reproducible after 18 min of equilibrium. The decomposition of selenourea standard material and non-fluorescent characteristic of selenate made their analysis challenging along with other analytes. The online UV irradiation for the digest and subsequent destruction of organic compound structure was carried by using 5 m long PTFE tube rounded around the ultraviolet digestion lamp (15 W). The proposed method was successfully applied to estimate selenium compounds in selenious yeast tablet, urine and environmental and biological samples (Liang et al., 2006, Mazej et al., 2006, Wei et al., 2008).

Since the start of industrial age, the anthropogenic are eliminating mercury as a result its ubiquitous presence in various areas such as water sources, food chain, plant and fish is of global concern. In addition, mercury is mainly existing in multiple form such as inorganic (Hg^{2+}), elemental (Hg^0), and organic specie methylmercury ($MeHg^+$). Methylmercury is

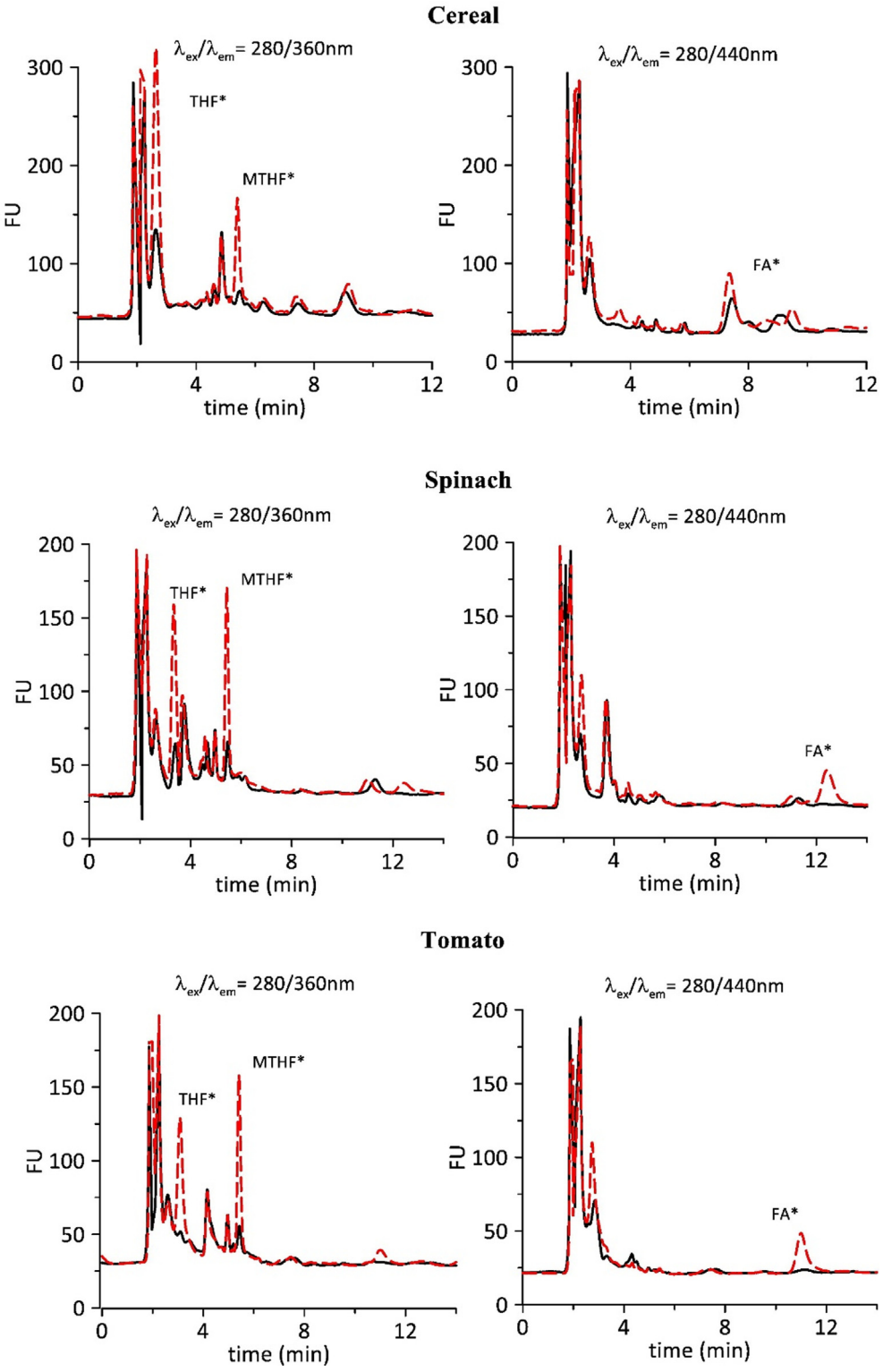

Fig. 9 Chromatograms of extracted and purified unspiked samples (black) and spiked 200 ng/nL standard solutions of THF, MTHF and FA (red dashed line). From (Martín Tornero et al., 2017) with permission from Elsevier.

classified as most toxic species and growing natural and human activities are converting mercury into organic mercury (methylmercury). The organic form of mercury especially methylmercury is causing various problematic disease such as neurotoxin, problems in early development of children, and neurological disorders in the prenatal stage. The European Food Safety Authority (EFSA) suggested the pregnant women to avoid the consumption of fish from top of food chain such as sword fish, tuna because of the high concentration of methylmercury. That's why EFSA and European regulation

states set the tolerable weekly intake of 1.3 μg/kg and 1 mg/kg, respectively in sea food (de Quadros et al., 2014, Lancaster et al., 2019).

Therefore, a specific method for the speciation of mercury was developed by coupling of PIF-HPLC-AFS for the determination of inorganic mercury, methylmercury and ethylmercury. In this system UV interface assisted to breakdown organomercuric species to inorganic Hg (II) and reduced it to volatile Hg (0). Under optimized chromatographic condition the target analytes were isocratically separated on Dionex Omnipac PAX-500 column. The proposed method involved the post-column mixing with formic and microwave assisted UV irradiation to decompose organic mercury specie into inorganic Hg(II) for separation and detection with fluorescence spectrometry. Proposed method various parameters including kind of organic acid, concentration, mobile phase composition, microwave power, and catalytic characteristic of TiO_2 nanoparticles were optimized for better sensitivity. It was observed the atomic fluorescence signals intensity for all-mercury species except 4-hydroxymercuric benzoic acid (pHMB) enhanced as the microwave power and concentration of used organic acid increased. The pHMB abnormal behavior can be attributed to the difference in mercury containing substrate, while high fluorescence intensity of other analytes is due to increase in generation of reactive radical that react with analytes to produce volatile species. The low sensitivity in case of acetic acid can be related to formation of limited concentration of radicals that discourage the photochemical generation of volatile mercury species. Whereas, formic, malonic and citric acid entailed highest AF signals at the irradiation time of 20 s. Therefore, the developed method exhibited excellent LOD in the range of 0.15–0.35 μg/L for all three mercury analytes and it was efficaciously used to analyze three certified reference material, and it proved superior method to conventional tetrahydroborate (THB) system (de Quadros et al., 2014).

Another, method was developed based on photochemical reduction method by LC-AFS for the determination of speciation (methylmercury) in hair and seafood matrices. The extracted samples were separated on reverse phase column prior to post-column UV irradiation-based reduction of methylmercury. Subsequently, mercury vapors are separated by purging argon through a gas–liquid separator to carry these for their quantification in the atomic fluorescence spectrometer. This method appeared simple and cost-effective as number of reagents required are minimum only methanol and acetic acid for separation and reduction of Hg into Hg^0, respectively. It was also compared with conventional vapor generation method for similar sample matrices and LC-PVG-AFS method appeared more sensitive with much lower LOD and precision (Lancaster et al., 2019).

4. Future perspectives

Although liquid chromatography hyphened to photoinduced fluorescence detection system is undoubtedly a treasured addition for the sensitive analysis of a variety of organic compounds in a wide range of sample matrices. But the future reliability on LC-PIF-FLD method will be counted basically to the official analytical protocols and well-established methods that are currently being used in everyday routine. Therefore, it is important to further calibrate this technique in order to fulfill the growing challenges, demands and keep up the pace with other techniques such as LC-MS. Few opinions in this direction that have to be addressed are as follows;

i. Analytes at trace level concentration (micro & nano) are un-noticeably inflicting serious health problems to human being, therefore, it is pertinent to upgrade this method (LC-PIF-FLD) into extra advanced, environment friendly and sensitive method for the analysis of target analytes at trace stage in complex pattern matrices. Miniaturization of this approach is one conceivable step for its application in food, biological, environmental, forensics, omics, and clinical fields. This miniaturized approach will now not solely turn out to be portable, however, will be in a position to limit or reduce the utilization of organic solvents and eluent that can lead to higher reproducibility, portability, green, and affordable for the analysis of target analytes in wide range of matrices (Rocha et al., 2015).
ii. The LC-PIF-FLD shall be held up with the present-day instrumental advancement. For instance, a simple change such as coupling of miniaturized flow reactor with capillary LC can considerably minimize the target peak broadening with better reproducibly and robustness. Moreover, with small change in operation condition such as sample volume, flow rate, gradient program, and eluent consumption can appreciably limit the dead quantity and analysis time along with dead volume in order to acquire the required performance.
iii. A massive room is reachable for the use of exclusive novel stationary phase section to develop new analytical LC-PIF-FLD techniques to analyze polar and non-polar compounds in wide range of sample matrices.
iv. The advanced and developed commercially accessible LC-PIF-FLD setups shall be launched to increase its availability in most of the laboratories for routine use. For instance, an advance and improved on-line microwave-assisted photochemical reactor exhibiting higher performance in comparison to the conventional UV lamps (Zacharis and Tzanavaras, 2013).
v. There is need to introduce catalytic PTFE tubing to minimize the photo irradiation time form mins to seconds for a number of intrinsically non-fluorescent analytes.
vi. Numerous non-fluorescent analytes having neither chromophores nor fluorophores
vii. are challenging to detect via the usage of indirect or direct LC-FLD methods. However,
viii. photosensitized fluorimetry ought to overcome this limitation. As low temperature
ix. phosphorescence and room temperature phosphorescence haven't been completely realized for the detection of analytes because of complicated sampling condition. Besides, a number of spectral techniques such as variable perspective scanning spectra, derivative, and statistical treatments such as partial least squares regression (PLS) ought to help to interpret PIF alerts of analytes in complex samples. Hence, it is handy to say that further advancement in versatility, selectivity and sensitivity of fluorescence methods will definitely help in

making it a better technique for a broader use towards various analytes (Carretero et al., 2005, Oar et al., 2005, Icardo and Calatayud, 2008, Astrath et al., 2010, Rocha et al., 2015, Muhammad et al., 2021).

x. The matrix effect is a serious drawback of spectrophotometric approach together with LC-PIF-FLD to analyze target components in complex samples extracts. If the traditional sample pretreatment approach is not effective to eliminate the matrix interferences, then matrix impact can severely affect the estimation of component of interest, results in bad analytical figures of merits. Therefore, it would be effective to introduce and couple online sample pre-treatment systems with the pre-existing LC-PIF-FLD setup in order to eliminate or minimize the matrix interferences. For this purpose, two and three-dimensional hyphenated chromatographic systems have been proposed. This online multi-dimensional device would now not only be able to significantly reduce matrix interference, labor, analytes loss, and operation error, but can also be able to enhance the accuracy, sensitivity and selectivity of the developed technique.

xi. The application of LC-PIF-FLD technique needs to expand for the determination and identification of unknown compounds especially natural products and fluorescent active photoproducts. For this purpose, it is pertinent to incorporate characterization and structural elucidation of these unknown compounds in the sample extract. Therefore, LC-PIF-FLD technique needs to be upgraded and hyphenated with mass spectrometry for the characterization of these unknown compounds.

5. Concluding remarks

In liquid chromatography post-column photochemical derivatization-based fluorescence analysis has offers a number advantages over chemical derivatization such as simple, cost-effective, online, efficient and reproducible derivatization. It has overcome the limitations of the conventional LC-FLD approach including increased its applicability range, enhanced the detection sensitivity, and improve the selectivity. There is a continuous improvement in reactors coil tube, lamp, and even the size of the system has been set since its introduction. Consequently, this application-oriented technique has made it possible to establish inexpensive methods to determine pesticides, drugs, contaminates, organic acids, metals etc. in simple to complex matrices by complementing with an appropriate sample preparation method. This review provides argument and justifications in support of LC-*hv*-FLD system devoid the expensive MS technique, which isn't available in laboratories of most of the developing countries. Therefore, the efficient and reproducible UV irradiation-based derivatization methods are becoming method of choice for the quantitation of analytes at trace level (nanomolar, nanogram) from food, biological and environmental samples due to its excellent sensitivity, specificity, robustness, lower LOD, and no matrix effect. Moreover, online sample pre-treatment, fabrication of portable and miniaturized technique along with identification of fluorescent active photoproducts are topics of interest for the accurate and sensitive quantification of targeted non-fluorescent analytes in complex sample matrices. We envisage a significant increase in the applications of this photochemical derivatization-based LC-FLD technique for determination of known and unknown analytes in widespread areas in the future.

Declaration of Competing Interest

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

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Ethical approval

This article doesn't contain any study on human/animal participants. The authors confirm compliance with ethical standards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.104091.

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