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Flow-injection analysis as a tool for determination of pharmaceutical residues in aqueous environment

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ABSTRACT

Numerous reported applications of flow-injection analytical methods in pharmaceutical analysis concern quality control of pharmaceutical preparations, investigation of dissolution of particular formulations and process control of production of pharmaceuticals. In recent decades an important environmental problem is increasing level of pharmaceutical residues in aqueous environment. The analytical determination of those residual compounds requires of the use a very selective method of a very low limit of detection. Appropriate selection of extraction and preconcentration methods for on-line sample processing and suitable detection allows the development of flow-injection analysis methods for such analyses. Especially satisfactory for this purpose is the application of a measuring system combining flow-injection systems for on-line sample processing with liquid chromatography.

1. Introduction

Flow analysis methods are being developed for the mechanization of various analytical methods which are employed in different areas of routine chemical analysis since 1950s. Since the beginning of this development, and especially since invention of different versions of injection methods of flow analysis, their principal attribute is improvement of the performance of analytical measurements by development of various methods of on-line sample processing and use of practically all instrumental detection methods of modern chemical analysis. The flow of the analyzed sample through the detector during the measurement allows in certain cases a favorable improvement of functional properties of the detector. The carrying of sample processing operations in flow mode allows improving their efficiency and reproducibility. These factors in terms of continuously increasing requirements addressed to modern chemical analysis ensures a strong position of flow analysis methods in the development of new methodologies in routine applications in various areas.

The development of flow analysis takes place simultaneously with permanent progress and improvement of whole analytical instrumentation. This proceeds also parallel to invention of entirely new concepts of carrying-on the analytical measurements of different mechanization degree and integration of different elements of measuring system, or its miniaturization based on the use of current developments in electronics, material science, or informatics. It has to be admitted also, that there is still open way to instrumental setups which are fully automated, where currently used operational parameters are being adjusted in real-time mode by appropriate system equipped with artificial intelligence, based on the use of feed-back loop interactions of all elements of the measuring system.

The instrumental evolution of analytical flow measurements and whole instrumentation for chemical analysis are strongly associated with fluctuations of the interest in the use of those methods in different fields of practical applications. Initial wide interest in application of first flow analyzers in routine clinical diagnostics is later on replaced by their wider use in environmental analysis, food analysis and process analysis. Those later areas are also the main field of increasing practical applications of injection methods of flow analysis, which is evident from increasing list of methods accepted as reference methods by various national and international authorities [1]. In recent years one can observe a successful transformation of flow analytical methodologies into

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a microfluidic format, which may potentially open a substantial new field of practical applications of flow analysis concept.

A field of chemical analysis, which is still not sufficiently explored for employing of the flow-injection analysis (FIA) and its various variants is the determination of trace organic pollutants in environment. Numerous such applications have been already reported, *e.g.* for determination of pesticide residues with biosensors used as detectors in flow systems [2]. Determination of individual trace organic analytes requires, however, the use of specific immunosensors as detectors. In practice, for such purpose a multicomponent chromatographic and electromigration methods are commonly employed with sensitive luminescence and mass spectrometry detection methods. Those methods are also predominant in determination of pharmaceutical residues in environmental samples, *e.g.* [3–8]. As the most sensitive and simultaneously providing a relatively rapid screening tools for determination of grace organic pollutants are considered enzyme-linked immunosorbent assays (ELISA) [9]. The alternative application for this purpose of properly optimized flow-injection method, requires a development of suitable method of on-line sample processing, and the use of a very sensitive, and preferable selective, method of detection.

2. Pharmaceutical residues in the aquatic environment

With commonly observed in recent decades increase of use human and veterinary pharmaceuticals one can observe also an increase of the presence of their residues in the environment. This fact together with a finding of synthetic pharmaceuticals in finished drinking water causes an increasing concern about potential environmental and health harmful effects. The most commonly accepted form of toxicity associated with environmental pharmaceutical residues is endocrine disruption, which means the disruption of chemical signaling mechanisms controlling cellular development [10].

First reports about detecting pharmaceuticals in environmental samples were published in early 1970s [11], and in 1965 it was observed for the fist time, that residues of steroid hormones are not completely decomposed by wastewater treatment [12]. Since then a fast increase of interest in different aspects of presence of pharmaceutical residues in environmental waters is observed. Number of papers published annually was about 500 in 2000, while it reached the level of about 3000 in 2010 [13]. In recent decade this problem was a subject of several published books, *e.g.* [14–16], and numerous valuable review articles in scientific journals, *e.g.* [10,13,17,18].

Pharmaceuticals are very large and diverse group of chemicals consisting of both human and veterinary medicinal compounds. It is assumed that it consists of about 4500 species, including pharmaceuticals which are in various stages of investigation. The US Food and Drug Administration approved in 2005 a 1090 small molecule drugs [19]. Research studies concerning their presence in environment and their removal from waters and wastes published so far, deal with about 160 human and veterinary pharmaceuticals and about 30 by-products [18]. The main groups of pharmaceuticals, which are detected in aqueous environment include anti-inflammatory drugs (analgesics), steroids and related hormones, antibiotics, β-blockers and lipid regulators [19]. Some of them are consumed annually even in tens or hundreds of tons. For instance non-steroidal anti-inflammatory drug paracetamol – 622 t in Germany in 2001, ibuprofen – 345 t in Germany in 2001, diclofenac – 86 t in Germany in 2001, and naproxen – 35 t in England in 2001 [20].

As the main source of wide presence of pharmaceuticals in environment is considered municipal water discharge, of which many residual drugs are not removed by a current wastewater treatment processes. Another contributing sources are industries, farms and hospitals, although as it was demonstrated recently by studies carried out in Norway, the point sources discharges from hospitals typically make a small contribution to the overall pharmaceutical loading in comparison to municipal sources [21]. Many pharmaceuticals are excreted mainly as metabolites and hence their presence in aquatic environment. A significant element of these environmental processes is also indirect potable water reuse. Waste waters treatment plant discharge is directed to surface waters, and in some cases effluent dominated surface waters are used for drinking treatment facilities. The complexity of circulation and transformation of pharmaceuticals, contributing to their presence in environment is well illustrated by scheme in Fig. 1, reproduced from the review paper by Petrovic et al. [22].

Besides increasing consumption of pharmaceuticals, a significant factor contribution to their presence in environment is limited efficiency of their decomposition in wastewater treatment plants, and in drinking water treatment plants. This concerns such methods as UV irradiation, oxidation with free chlorine, or even ozonation [23]. Concentration of some pharmaceuticals detected in effluents (antibiotics, non-steroidal anti-inflammatory drugs or steroid hormones) may reach even fractions of mg/L [24]. This is then reflected by concentration s of pharmaceuticals and their metabolites in worldwide tap water, which are found in some cases in the level exceeding 1 μg/L (iodinated X-ray contrast medium diatrizoate, analgesics AMIDOPH, ibuprofen) [25]. Hence, strong attention is focused in recent years on development of radical methods of decomposition, described as Advances Oxidation Processes [26]. Especially efficient process is radiolytic decomposition by the use of ionizing radiation (γ or beam of accelerated electrons), where as result water radiolysis taking place during irradiation of aqueous solutions radicals of oxidative and reductive properties are formed. These processes were already examined for satisfactory decomposition of β-blockers [27], and antibiotics nitroimidazoles [28].

Frequent occurrence of pharmaceuticals in aquatic environment, and also in finished drinking water, is a source of concern about their impact on public health, although commonly encountered opinion in the literature is that our current knowledge what is effect of human exposure to low-dose mixture of pharmaceuticals is none [10]. One can find opinions about no appreciable risk to human at detected concentrations of pharmaceutical residues [29], but due to consuming contaminated drinking water over a lifetime, chronic toxic effects cannot be excluded because of lack of chronic ecotoxicity data [30]. This creates both demand for wide monitoring of presence of pharmaceuticals in waters and wastes, and search for more efficient and cost-effective methods of their removal.

3. Flow-injection analytical methods in pharmaceutical analysis

Pharmaceutical application of various variants of flow-injection analysis is an important field of development of theses methods with possibilities of application in routine analysis. A degree of difficulties in development of such methods depends mostly on matrix of analyzed samples, in which particular pharmaceuticals is determined, on selectivity of used detection method, and a concentration level on analyte in analyzed sample. The choice of particular variant of flow-injection methods is determined mainly by sample processing methods which will be employed for particular sample, requirements of sample and reagent consumption, and possibilities of mechanization of whole measuring setup.

The development of FIA methods for determination of pharmaceuticals can be dated back to the early years since their invention. One of the first example methods can be determination of penicillins with potentiometric detection of pH changes using

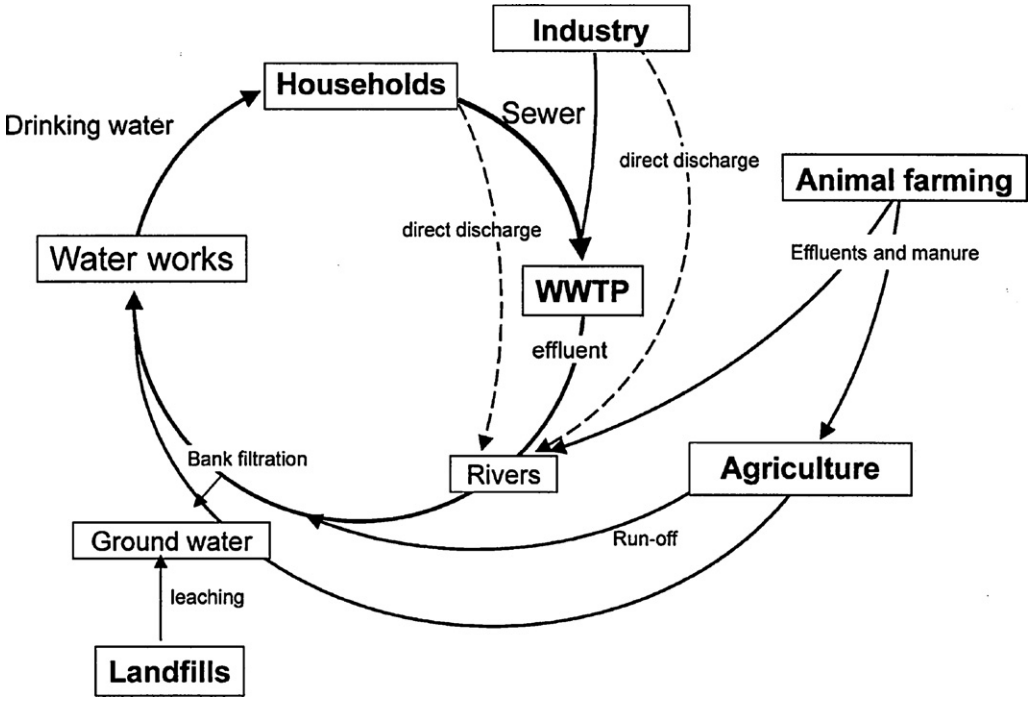

Fig. 1. Schematic diagram of water cycle showing sources and transformations of pharmaceuticals in natural environment, where one of the main sources is untreated urban wastewaters and wastewater-treatment plants (WWTP) [22].

immobilized penicillinase in a single bead string reactor [31]. Penicillins G and V were determined in the submillimolar range in pharmaceutical tablets, injectables, and fermentation broth. Further fast progress in this area of applications is well illustrated by monograph published in 1996 by Calatayud [32]. The progress made in recent years is well documented in reviews published in last decade [33–37], as well as dedicated Chapters in recently published books [38,39]. They report application of FIA [34,38,39] and sequential injection analysis (SIA) [37] with different detection methods for determination of pharmaceuticals, as well as application of FIA methods with spectrophotometric detection, only [35]. The main applications are focused on the quality assurance of pharmaceutical preparations, where those methods can effectively compete with commonly employed standard methods. Other fields of pharmaceutical applications of flow injection methods include process analysis concerning the control of production process of pharmaceutical preparations, and also studies of changes of composition of preparations during their storage.

Another important section of applications of FIA methods is monitoring of drug dissolution, providing information about dynamic properties of different formulations of particular drugs [33]. Such determinations carried out in flow analytical systems allow mechanized use of various method of sample processing such as on-line filtration, microdialysis, or solvent extraction. These methods can be effectively combined with chromatographic, electrophoretic, or in indirect determinations with atomic spectroscopy detections. In such determinations also a dedicated potentiometric membrane electrodes can be employed, where selectivity of detection is not a most crucial issue [40]. Both determinations of content of active substances in pharmaceutical preparations, and in drug dissolution testing do not require usually the use of methods of especially low values of limit of detection.

As alternative to chromatographic or electrophoretic methods there are attempts to develop flow injection multicomponent methods [37]. For this purpose one can utilize optical methods based on recording spectra in a wide wavelength range and appropriate processing of experimental data. For instance, with the use of photodiode array detector and recording normal and derivative spectra mixtures of etafedrine hydrochloride, phenylephrine hydrochloride, doxylamine succinate and theophylline were analyzed [41]. Determinations were carried out in concentration range 0.05–0.12 mM and successfully applied for analysis of pharmaceutical preparation. In another example, in stop-flow measurements, using Fourier transform infrared spectrometry with partial least-square data treatment, a mixtures of paracetamol, acetylsalicylic acid and caffeine [42]. Determinations carried out at concentration level 0.3–3.3 mg/mL were successfully employed also for analysis of pharmaceutical preparations. Concentrations of analyzed species determined in mentioned works are few order of magnitude higher, however, than those expected in determination of pharmaceuticals in environmental samples.

A much closer to potential applications in environmental analysis are FIA methods developed for determination of pharmaceuticals in complex matrices of physiological fluids and foods. Optimization in those cases is focused on obtaining much lower values of limit of detection (LOD). Numerous examples of such applications can be already found in cited above reviews [32–39]. Especially satisfactory for this purpose is the application of FIA methods with sensitive luminescence detections. For instance, the FIA method with chemiluminescence (CL) detection employing ion-pair complex-based solvent extraction was developed for determination of chlorpromazine, widely used for treatment of clinical depression [43]. This method with LOD 6 ppb was successfully used for analysis of human urine, but for application in environmental samples much lower LOD is required [44]. The same CL detection was employed in FIA determination of a common non-steroidal anti-inflammatory drug naproxen in urine [45], which in environmental samples was found even at such high as 7.8 ppb level [26]. As LOD in mentioned work was evaluated for 10 ppb [45], the additional application of effective preconcentration step might be sufficient for environmental application of that method. In case of common non-steroidal anti-inflammatory drug ibuprofen, its level in environmental samples was reported even at fraction of ppm level [26]. The developed FIA method with CL detection reported

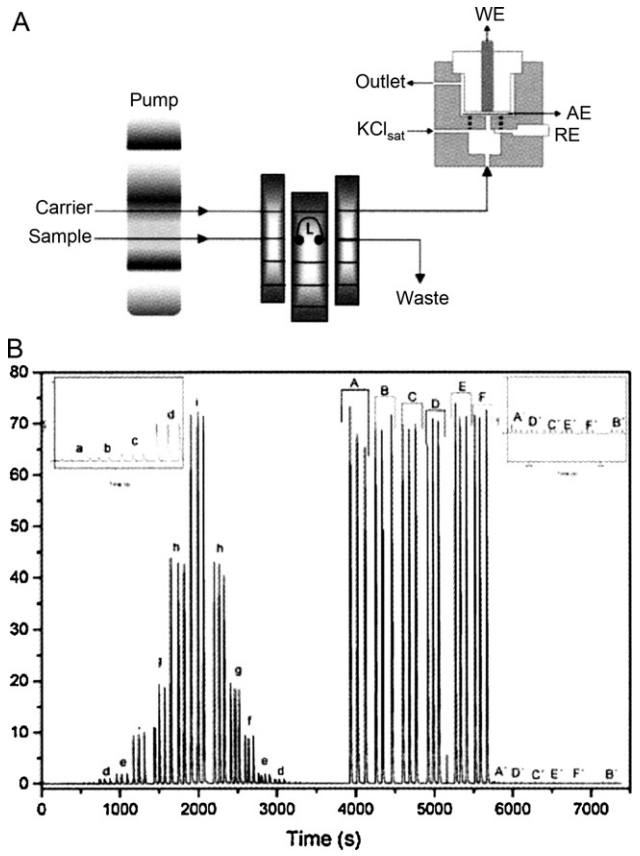

Fig. 2. (A) Schematic diagram of flow injection system with amperometric detection for determination of paracetamol: WE, working electrode; AE, auxiliary electrode; RE, reference electrode. (B) Flow-injection response obtained for calibration and for measurements of six river water samples enriched with paracetamol at 50 mM level (A–F), and 0.1 mM level (A′–F′) [51].

for determination of ibuprofen in human urine samples with LOD at 30 ppb [46] seems to be applicable to environmental samples. The FIA method with fluorescence detection was developed for determination of commonly employed anticonvulsant carbamazepine in human plasma [47]. This is one of the most commonly encountered drugs in aqueous environment, even at few ppb levels [48]. In the mentioned method developed for determinations in human plasma, which is based on use of a solid-phase reactor with PbO_2 for on-line oxidation of analyte to fluorescent product LOD was reported as 0.057 ppb, hence this method seems to be satisfactory for determination of carbamazepine in environmental samples.

Another area of pharmaceutical applications of FIA methods is functional cellular assay for screening potential drugs. Such measurements are carried out for the identification and characterization on new drugs based on functional test allowing to determine their biological response. If drug is binding to a cell receptor, it may result in change of various parameters, which can be measured as, *e.g.* intercellular pH changes, glucose or oxygen uptake, or a release of cytosolic calcium. For instance, for examination of cellular responses SIA bead injection system was reported with fluorimetric detection of intracellular calcium [49]. In another approach the lab-on-valve methodology was used also with bead injection to assess the glucose uptake by living cells, with a two-step enzymatic detection of glucose [50].

4. Flow-injection analysis for determination of pharmaceutical residues in environmental samples

Environmental danger of pharmaceutical residues results in widening interest in development of effective and automated systems for determination of those compounds in environmental samples. As it was shown above on several examples some methods developed for trace determination of pharmaceuticals in complex matrices of physiological fluids might be possibly applied also in environmental applications. Number of flow-injection methods developed so far for authentic environmental applications are rather limited, and they will be reviewed below, but one can expect quick increase of interest in development of such methods.

In papers published so far different configurations of flow systems were reported and with different detections, which significantly contributes to obtained limits of detection in optimized procedures. In simple FIA system (Fig. 2A) reported for determination of paracetamol, a common antipyretic and analgesic drug, the amperometric detection was employed [51]. In three-electrode measuring system as working electrode a glassy carbon electrode was used, which was modified with Nafion membrane doped with iron tetrapyridinoporphyrazine, acting as catalyst mimicking activity of P450 enzyme. At obtained LOD 1 μM the possibility of paracetamol determination was examined in river water spiked at

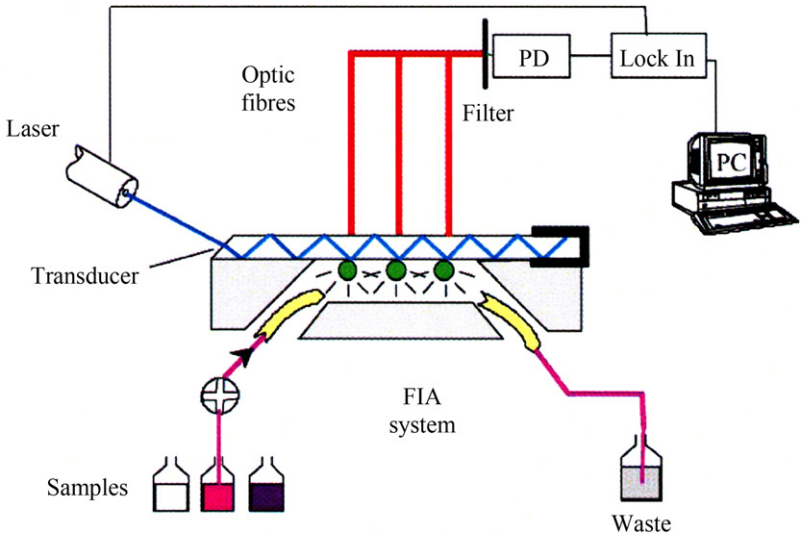

Fig. 3. Schematic diagram of flow-injection system with immunoassay detection RIANA based on total internal reflection fluorescence with immobilized fluorescently labeled antibodies [52]. The source of the excitation light is a He–Ne laser, and the collected fluorescent light is filtered and detected by photodiodes (PD).

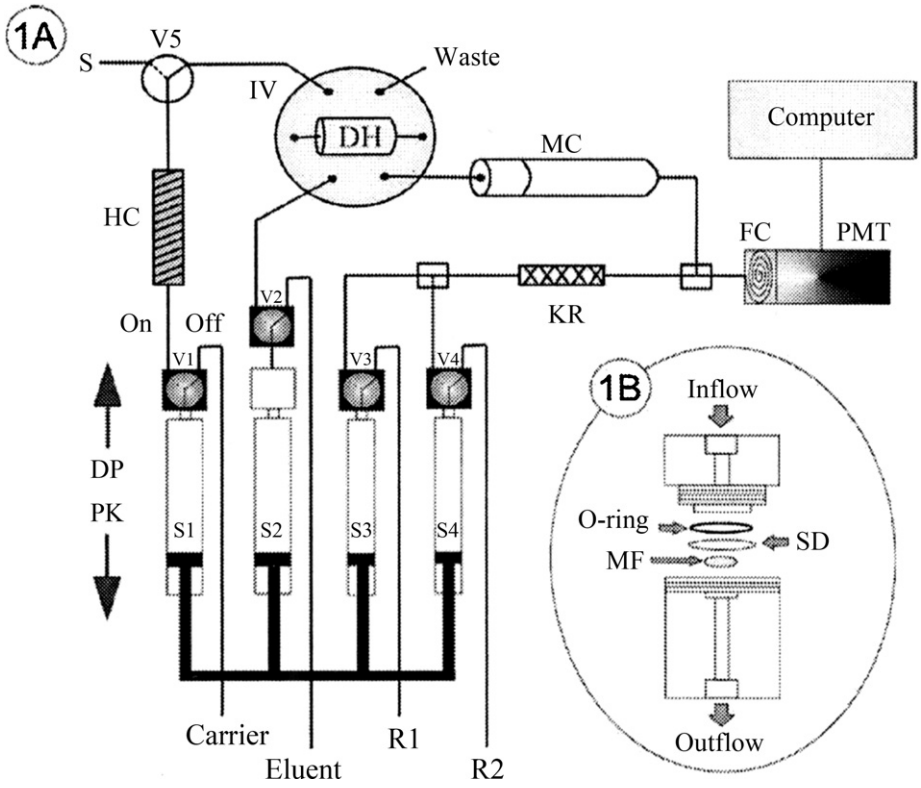

Fig. 4. The multisyringe based flow-injection system (1A) for determination of thiazide compounds with chemiluminescence detection, on-line solid-phase extraction using sorbent disk in disk holder (1B) and separation on monolithic chromatographic column (MC): DH, disk holder; KR, knotted reactor [53].

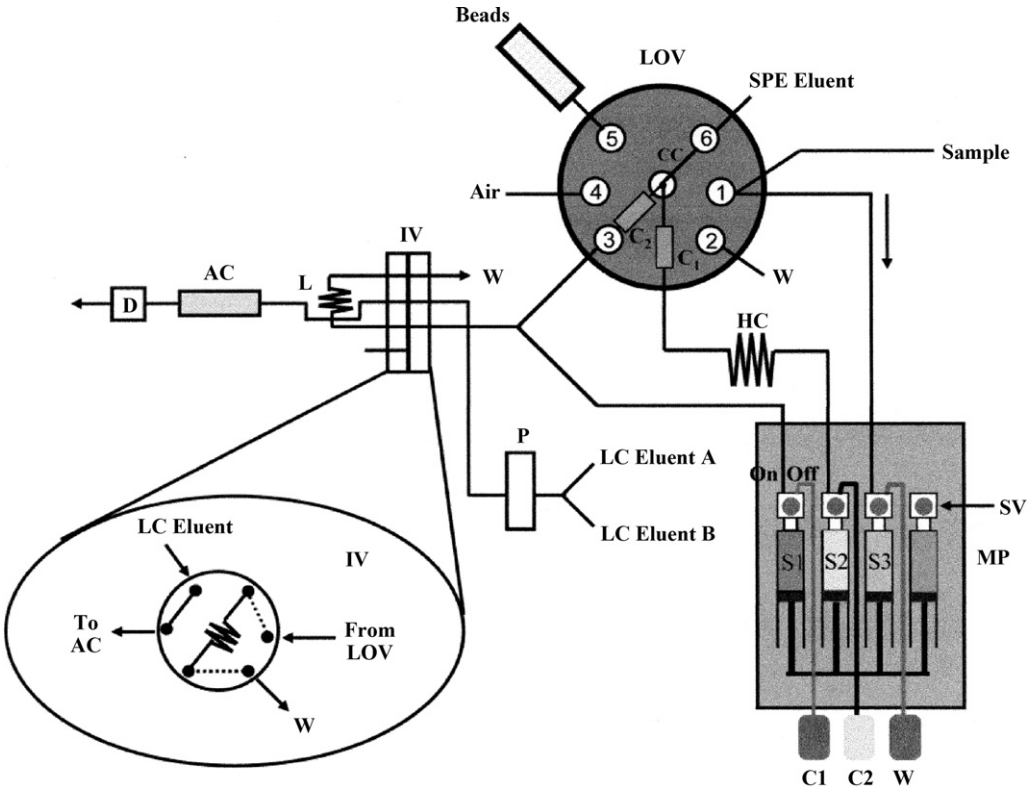

Fig. 5. The multisyringe flow-injection system using lab-on-valve Oasis HLB bead injection hyphenated to HPLC separation on reversed phase column and UV detection for determination of acidic drugs [55]: LOV, lab-on-valve injection device; MP, multisyringe pump; HC, holding coil; P, HPLC pump; AC, analytical column; D, detector.

rather high concentrations 50 and 0.1 mM (Fig. 2B), demonstrating obtaining satisfactory recovery values. For most expected authentic environmental applications, however, the determination should be preceded with effective step of analyte preconcentration.

In other reported flow methods for determination of pharmaceutical residues in environmental samples the optical detections were employed. For the detection of selected pesticides, but also natural estrogen estrone in water the FUIA system was developed with detection using immunosensor based on total internal reflection fluorescence [52]. In applied detector a laser beam is guided through transducer by total reflection (Fig. 3). An evanescent field produced by each reflection spot causes the excitation of fluorescently labeled antibodies that are bound to the analytes. Without additional preconcentration, the limit of detection fro estrone was achieved as 84 ng/L. The evaluation of the matrix effect was carried out for ground and river waters, and also for wastewater, showing that application of developed system only to more complex matrices like wastewater seems to be importantly restricted. Determinations reported for river water spiked with 0.1–2.0 μg/L estrone show good correlation with LC–MS analysis.

The sensitive chemiluminescence detection was employed in flow system for determination of diuretics, which are group of pharmaceuticals used against hypertension and heart or renal failure [53]. The determinations were carried out in flow system where a multisyringe flow injection part was employed for solid-phase extraction (SPE) of analytes on extraction disks and was hyphenated to chromatographic separations on a reversed-phase monolithic porous silica column functionalized with octadecyl groups (Fig. 4). The chemiluminescence detection was based on reaction of analytes in knotted reactor, place in front of photomultiplier tube, with tris(2,2′-bipyridylruthenium (III)), generated in redaction of $[Ru(bipy)_3]^{2+}$ with cerium (IV). The best performance in SPE step was found for poly(styrenedivinylbenzene) disks, modified with sulphonic groups. The separation of three determined thiazide compounds was obtained in 3 min run with LOD in the range 3–40 μg/L. The developed method was assessed by analyzing a well water spiked with 2–20 μg/L analytes. For real environmental applications the LOD values should be, however, rather at ng/L.

Several similar applications were reported for flow systems with common spectrophotometric detection in UV range. In the system with similar design as reported above [53], the determination of antihypertensive agent hydrochlorothiazide and losartan potassium, a non-peptide angiotensin II receptor antagonist was developed [54]. In this case enrichment of analytes was carried out on a Cation-SR sorbent material in multisyringe flow injection system, which was followed by reversed-phase chromatographic separation on monolithic column with indirect UV detection. The LOD was evaluated as 70 and 90 μg/L for hydrochlorothiazide and losartan potassium, respectively, for sample loading 1.0 mL. The developed method was applied in analysis of superficial water, ground water and wastewater outlet spiked up to 1.0 mg/L level of analytes. Much lower values of limits of detection (0.02–0.36 μg/L) were achieved in determination of residues of five acidic pharmaceuticals ketoprofen, naproxen, bezafibrate, diclofenac and ibuprofen [55]. In this case HPLC separation on reversed-phase column was hyphenated to flow injection lab-on-valve system with preconcentration on renewable sorbent beads Oasis HLB (Fig. 5). Chromatographic detection was carried out with UV detection. The satisfactory recoveries were obtained by analyzing 18 mL surface water sample spiked up to 0.4 and 1.0 μg/L level, and also raw and treated wastewater spiked up to 10 and 40 μg/L. Among various literature data on highest residue content of those pharmaceutical in waters and wastes [18,22], only in case of ibuprofen a higher residue levels were reported, than LOD of this method [55].

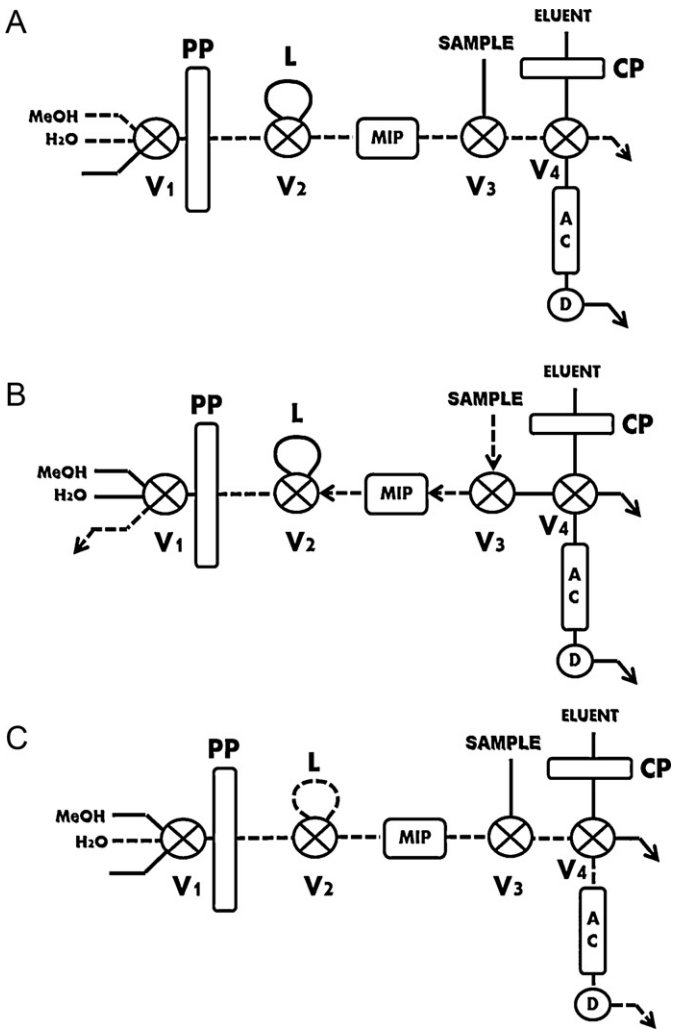

Fig. 6. Schematic diagram of hyphenated FIA-HPLC system with UV detection and on-line preconcentration on MIP column for determination of chloramphenicol [57]. Setting of the system for washing (A), sample loading (B), and sample elution for injection into HPLC system (C): PP, peristaltic pump; CP, chromatographic pump; V_i, injection valves; AC, analytical column; MIP, flow-through reactor with molecularly imprinted polymer; D, detector.

In different analytical applications of solid-phase extraction method an increasing interest is focused on molecularly imprinted polymers (MIP) as affinity-based separation media for sample preparation [56]. They can be also employed as recognition elements in sensors, as highly selective stationary phases in liquid chromatography, or pseudo-stationary phases in capillary electrochromatography. An attempt on their application was also reported for determination of trace residues of an antimicrobial agent chloramphenicol in environmental samples [57]. It was shown that in simple FIA system with UV detection and microcolumn with MIP the sorption/elution process for chloramphenicol (CAP) is not sufficiently specific and obtained LOD too high in order to apply this method for trace residue determination of CAP in environmental samples. Hence for this purpose a hyphenated measuring system was designed, where FIA system with MIP microcolumn was combined with HPLC system with UV detection (Fig. 6). The optimization of such system involved both chemical conditions of preconcentration and elution of CAP in order to get satisfactory recovery and compatibility with HPLC conditions, as well as time of re-sampling, when after starting elution of CAP from MIP microcolumn the injection of 20 μL sample to HPLC should take place. For additional removal of matrix components non-specifically retained

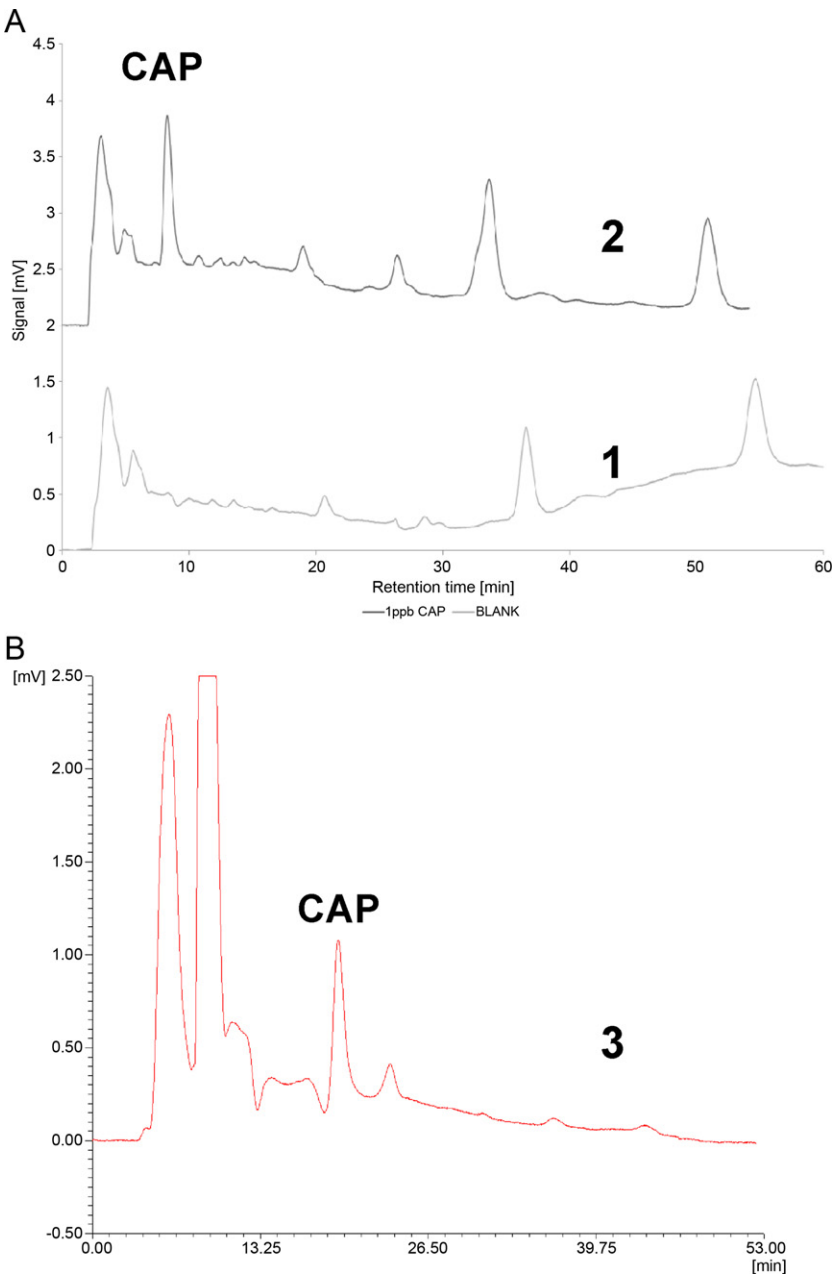

Fig. 7. (A) Chromatograms recorded in FIA-HPLC system shown in Fig. 6 for measurements of 100 mL river water without spiking with CAP (1), and with spiking with 1 μg/L CAP (2) [57]. (B) Chromatogram recorded in FIA-HPLC as in Fig. 6, but with MIP column replaced by immunosorbent flow-through micro-column, for 100 mL river water sample spiked with 1 μg/L CAP [58].

on the MIP, a washing step was introduced using acetonitrile solutions containing acetic acid and ammonia [58]. The example chromatogram obtained in FIA-MIP-HPLC system for river water samples spiked with 1 μg/L CAP is showed in Fig. 7A. The presence of other signals besides CAP in natural matrix proves the necessity of chromatographic determination with the use of commercial MIP for CAP determination in natural waters. For initial volume of water sample 100 mL, the LOD value was evaluated as 25 ng/L.

For comparison, in the same measuring system the MIP microcolumn was replaced by immunoreactor with anti-CAP antibody immobilized covalently on controlled porous glass [58]. The recorded chromatograms for raw and spiked water samples (Fig. 7B) indicate a little bit better selectivity for CAP determination in such system and LOD as 33 ng/L. Both application of MIP and immunosorbent in FIA-HPLC system for determination of CAP gives similar results. In case of MIP microcolumn about 30 samples were analyzed without changes of sorption properties, while in case of immunosorbent usually after 5–7 determination a changes of sensitivity of determination were observed. The obtained values of LOD might allow application of this method for CAP determination in some wastewaters, where CAP level reached even fractions of μg/L [59,60].

5. Conclusions

Although analytical literature contains hundreds of research papers reporting applications of flow injection analysis to determination of pharmaceuticals, the application of these methods in determination of residue pharmaceuticals in environment is a challenge undertaken in recent several years. It is difficult task,

requiring a very efficient preconcentration of trace analytes and use of sensitive and selective detection methods. The developments reported so far for this purpose indicate the possibility of such determinations in flow systems where on-line sample preparation is hyphenated with chromatographic measurements. One may expect, however, that wider interest in development of such important applications of flow injection methods will soon result in simplification of such measuring systems. This may lead to authentic, real applications of such measurements for control and protection of natural environment. Observed in recent decade miniaturization of FIA systems based on multicommutation and multipumping may lead to development of portable FIA systems for field applications in determination of pharmaceutical residues. On the other side, it seems that the hyphenation of FIA systems, incorporating on-line sample processing, with mass spectrometers may offer a valuable and simplified alternative to LC–MS instrumentation.

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