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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