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Review

Trends in sulfonamides and their by-products analysis in environmental samples using mass spectrometry techniques

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ABSTRACT

The sulfonamides were the first class of anti-infective agents discovered in therapy for the treatment of infectious diseases, even prior to the discovery of penicillin. Since their discovery, sulfonamides (SAs) are used in the human and veterinary medicine. Through the organic waste or manure utilization or other routes as discharge of effluent wastewaters into surface water, SAs could migrate to soil and water, affecting microbiota, fauna and flora. SAs are a ubiquitous group of drugs, widely detected in environment and specific resistance genes occurrence have been correlated with SAs presence. Thus, the development of robust and reliable method for SAs monitoring is of great concern. Trace and ultra-trace levels of SAs can be detected in several matrices. In order to achieve this level of detection sample preparation strategies combined with advanced mass spectrometry techniques as triple quadrupole, linear ion trap and time of flight mass detection associated with post-run strategies were currently used to SAs monitoring. In this work, a review of the most recent published reports, including the last five years, is presented.

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1. Introduction

The discovery of antibacterial activity of sulfonamides (SAs) was achieved in 1935 with the publication of the work "*A Contribution to Chemotherapy of Bacterial Infections*" [1], in which the biological activity of *p*-sulfamidocrisoidine (Prontosil Rubrum) was described by the german pathologist and bacteriologist Gerhardt Domagk. This substance had been synthesized in

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1932 by Mietsch and Klarer (Bayer), based on the classic chemistry of textile dyes, specifically to be tested as antibacterial [2]. The credit for this discovery gave Domagk the Nobel Prize for Medicine in 1939 [3]. After these years, other emerging antimicrobial substances were obtained, some synthetically and others isolated from microorganisms such as penicillin, discovered by Fleming in 1928, which showed severe bactericide action [2].

Forneau and co-workers detected the presence of sulfanilamide by analyzing metabolites in blood and urine samples of patients treated with Prontosil (*p*-sulfamidocrisoidine) [2]. Through this study they observed that the active part of the molecule was the sulfanilamide and that the various chemotherapeutic antibacterial hitherto well known, only acted because of the presence of the sulfonamidic pharmacophoric group, whose mechanism of action was subsequently established and related to the inhibition of the bacterial enzyme diidropteroate synthase.

Since the late 40s, other antibiotics replaced sulfonamides in chemotherapy because of their lower toxicity and broader spectrum of action [4] and even though the observation that certain bacteria showed resistance to antibiotics, a new interest for searching new sulfonamidic derivatives increased.

Nowadays, sulfonamides are used together with other antibiotics, e.g., sulfamethoxazole and trimethoprim to enhance their effects [5]. Moreover, new drugs have been derived from sulfamide rather promising as anticancer and antiviral drugs [6]. Recently, new applications have been demonstrated for the sulfonamides, e.g., diuretics, as well as new discoveries about their mechanism of action [7,8].

Despite the decrease in use in human medicine, sulfonamides are widely used in developing countries as basic medications, especially for urinary infections. Also to defeat *Plasmodium falciparum*, the causative agent of malaria, an association between sulfadoxine and pyrimethamine are widely used in affected zones [7].

Moreover, SAs are still widely used in veterinary medicine. Commonly, sulfonamides are used in food-producing animals to prevent diseases and treat infections. The incorrect administration of antibiotics in veterinary medicine has great potential risk that residues of these drugs may be present in edible tissue [9]. Also, the extralabel drug use as growth promotion is a possible source of SAs residues in food from animal origin [10]. Although several SAs are used simultaneously in human and veterinary medicine, some SAs present specificity for veterinary use, such as sulfaquinoxaline [11].

The main risk to human health of using antibiotics on animals is the fact that animal bacteria can develop resistance to drugs, mainly by using sub-therapeutic doses. This resistance can be developed by several pathways such as mutation, acquisition of resistant genes or a combination of both [12]. Recent reports demonstrate

The SAs can reach the environment through the discharge of effluent wastewaters into surface waters. Several studies have demonstrated that full removal of some of these compounds after secondary biologic treatment can be incomplete [13,14]. The lack of efficiency of current conventional wastewater treatment (usually by means of biological activated sludge (CAS)) has led to different researchers to consider treated waters as one of the main entrance pathways of these compounds into the environment and to link wastewater effluents to the presence of antibiotics in surface waters, sediments and soils. Another main route to SAs entry in the environment is re-use of animal manure and sewage sludge as fertilizer [15]. This subject has received increasing attention recently due to the fact that can be involved with the selective up-regulation of the so-called resistome of soil microorganisms [16,17].

On the other hand, ubiquity of the main metabolites of some SAs such as sulfamethoxazole, has been recently demonstrated [13,18]. Sulfonamides are not completely metabolized during use and are excreted into sewage, partly as unchanged parent compounds and partly as metabolites [19]. These metabolites, together with other transformation products that may be formed during the wastewater treatment and the different environmental degradative processes, can maintain the bioactivity and ecotoxicity of the original substance, and they can be even more active. For instance, N^4-acetylsulfapyridine was more bioactive against *Vibrio fischerii* than the original compound, sulfapyridine [13]. Another example would be the de-sulfonated product of several sulfonamides and their acetylated metabolites, which has been identified as the main transformation product in both biodegradation and photodegradation studies [20,21], accounting in some cases for the 80% of the initial concentration of the parent sulfonamide. However, there is no information regarding its environmental presence and/or ecotoxicity. All in all, data on the environmental fate and behavior of these metabolites and transformation products is still quite scarce, and therefore the inclusion of these metabolites in future research studies is crucial, as its oversight would lead to an underestimation of the real total concentrations discharged into natural waters and also to the ecotoxicity and water quality. Even though pharmaceuticals, only few antibiotics are considered in current legislation as priority pollutants [22]. Given the actual occurrence of these compounds in the environment, it is important to control their occurrence as well as the microbial diversity in strategic sites or potential hot-spots, in order to have more comprehensive information about water quality.

Analytical methods had enormous progress since 1980 decade. There were many scientific advances in sample preparation, analytical instrumentation, computerization and automation of all method stages. Many of these advances have been directed to increase the sensitivity and specificity of techniques.

The need to evaluate the environmental risk posed by drug residues came together with the development of instrumental analytical techniques able to detect these compounds at ultra-trace levels [20]. Metabolites formed in vivo or other degradation products of drugs are also a point of concern. The SAs group had relatively high water solubility. Besides, these compounds have a low ability to chelation. These characteristics associated with their amphoteric behavior provide high mobility, instead of locomotion capability for SAs in the environment [23]. SAsRegarding this issue, several methods have been developed in order to monitor SAs presence and biotic and abiotic degradation processes in samples including food, soil, wastewater, surface water, groundwater, sludge, manure, etc. [24]. The mass spectrometry (MS) techniques, especially the hyphenated modes, are very useful to this purpose and several reports had been published in recent years. The aim of the present work is to review the most recent available methods for the analysis of SAs in environmental samples using MS techniquesSAs. In Fig. 1, the growing interest in these topics is demonstrated by the number of articles published since 2003 sorted from the ISI Web of Science and SCOPUS using the keywords “sulfonamides” and “environmental”. Structures of the most common sulfonamides cited in this review are showed in Fig. 2.

2. Methods for SAs analysis in environmental samples

Tables 1–3 include a summary of recent significant studies regarding MS or MS/MS methods for the determination of SAs in environmental samples. These reports were classified according to the target compounds, sample characteristics, separation and detection techniques, sample preparation methods, detection limits (LOD) and data from method applicability.

For environmental samples, as soil, manure and water, extraction procedures are designed with the purpose of