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Studies of Human and Veterinary Drugs' Fate in Environmental Solid Samples—Analytical Problems

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Abstract

The improvement of medical care worldwide is one of the reasons for the increasing production of pharmaceutical products. Human medicines are affordable to a greater proportion of the world's population. But a significant amount of used pharmaceuticals can create problems—accessibility to high volume production pharmaceuticals contributes to an increased contamination in the environment and the possibility of adverse effects on humans and animals. Many of these substances and their metabolites end up in the soil, sediments, and sludge. Knowledge regarding the environmental occurrence of pharmaceutical products is increasing, but information in the peer-reviewed literature regarding the fate and effects of most pharmaceuticals is limited. One of the reasons for this lack of data is that, until now, there have been few analytical methods capable of detecting these compounds at the low levels, which might be expected in the environment. This review article covers recent developments in the analysis of pharmaceuticals in environmental solid matrices (including soil, sediments, and sludge). We will report applications of different solid sample extraction methods, and current advances in liquid chromatography coupled with mass spectrometry for detection and identification of selected drugs in sludge, soils, manure, and sediments.

Introduction

A range of pollutants have been measured at very low levels in different environmental compartments. A simple classification of pollutants is presented in Figure 1.

The schematic shows how pharmaceutical residues have become an important group of environmental pollutants. The production of pharmaceuticals is one of the most profitable and the fastest growing trades in the world. The world pharmaceutical market shows an incessant annual growth of 8%. The rapid pace of development in this sector is confirmed by the huge investment into research and development of new treatments; in Western Europe, in the year 2000, the outlay was approximately 16 billion USD, which was twice that spent in 1990. Over 70 million USD per annum is spent on pharmaceutical research worldwide on 100,000 different chemical substances, of which 30,000 products are marketed in quantities above 1 ton. (1) The largest part of European pharmaceutical production occurs in France (25 billion EUR), the United Kingdom (20 billion EUR), and Germany (19.6 billion EUR). The global pharmaceutical market is extremely fragmented, but the ten largest companies in the world represents more than 35% of the global market. Each of them employs about 50 thousand people and their products reach sales of billions of USD every year (1).

The main input of pharmaceuticals into the environment is through human and animal excreta. After application, many of these compounds and their metabolites are eliminated from the body mainly through the renal system (urine), biliary system (faces), or a combination of both depending on the nature of the compound and the organism in question (3,4). A large proportion of the active ingredient taken by patients passes through the body unchanged and travels via urine and faeces to waste water treatment plants (WWTPs) (5,6,7). Other potential source of pharmaceutical contamination are cattle feedlot effluents, agricultural run-offs as sewage, and manure used as fertilizer in certain countries. Finally, pharmaceuticals supplements are used in animal husbandry and aquaculture (Europe's consumption of veterinary drugs in 1999 was at the level of 1600 tonnes) (4,8,9).

During the last few years there has been an increased monitoring of pharmaceutical compounds in the environment. Numerous papers have reported trace levels of pharmaceuticals in wastewaters, surface waters, soil, and sediments. Due to a recent awareness of the potentially dangerous consequences of the presence of pharmaceuticals in the environment, the analytical methodology for their determination in complex environmental matrices is still evolving, and the number of methods described in the literature has grown. However, few examples of quantifying pharmaceutical residues in solid matrices have been published to date.

Fate and exposure routes of pharmaceuticals in the environment

Pharmaceuticals are a group of substances, which until recently, have been discharged to the environment with very little attention. One reason why there is concern for these environmental micro-pollutants, is that medical substances are, by their very definition, designed to induce a biological effect. The increased use of antibiotics in recent years has caused the

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genetic selection of more harmful bacteria. The genetic poll of micro-organisms in nature has changed significantly, simply due to increasing production and consumption of antibiotics. Using thousands of tonnes of animal and human medicines has a significant impact on the environment (10,11). Pharmaceuticals and their metabolites are incompletely eliminated in wastewater treatment plants and enter the environment and surface-water via industrial, hospital, and domestic effluents. The impact of medicines may be on any level of the biology hierarchy: cells → organs → organisms → population → ecosystems → the ecosphere. The modes of action of most pharmaceuticals in humans, animals, and fish are often poorly understood. Moreover, mixtures of drugs might lead to synergistic effects in the environment.

Methods of determination of pharmaceuticals in the environment have evolved significantly for aqueous and solid phases since they were first described as early as the late 1980s (2). Earlier investigations of drug residues in sewage treatment plant effluents were focused on clofibric acid, the major metabolite of the three lipid regulators (etofibrate, etofyllinclofibrate, and clofibrate). Clofibric acid has been detected in the lower µg/L level in treated wastewater in the United States, in the river waters of Great Britain at levels below 0.01 µg/L, in Spanish ground water samples, and even in drinking water in Germany at concentrations up to 0.27 µg/L in Berlin tap water (12).

An identification of the exposure route is crucial for estimating the corresponding environmental load determined by the dose of drugs and the duration of treatment. The same drug may be used for several applications (e.g., therapeutic treatment for pigs and in fish farms), resulting in a different dose and duration of treatment. Combined with different exposure routes to various environmental matrices, the fate of the drug may also vary resulting in quite different environmental concentrations (13).

The amount of a pharmaceutical excreted from the body varies with the compound, the individual, and the mode of action. It has been suggested that up to 90% of an administrated dose may be excreted through urine and faeces (14).

Today, we do not actually know the fate and effects of pharmaceuticals when they are discharged to the environment. After having a pharmacological effect in the body, a medical substance will be excreted through urine or faeces as a mixture of metabolites, as the unchanged substance, or conjugated with an inactive substitute, depending on the pharmacology of the substance of concern (15,16). They can also enter the environment through waste effluents of manufacturing processes, disposal of unused or expired medicinal products, and accidental spills during manufacturing or distribution. The drugs used by humans will be discharged to sewer systems in urine and faeces and enter the sewage treatment plant. Digested sewage sludge can be used as a fertilizer on agricultural fields, contaminating soil with human pharmaceuticals. Moreover, other factors can lead to the occurrence of drugs in soil (e.g., the use of treated wastewater to irrigate fields, flooding of fields with receiving waters containing appreciable proportions of treated wastewater) (13).

Most of the veterinary pharmaceuticals end up in manure. The urine, faeces, and manure are either stored or immediately applied to agricultural fields as fertilizer. The conservation period and field immersion standards, depends of legislative regulations on a national level. When manure is spread on a field, the unmetabolized drugs present in the manure (or their biologically active metabolites) may threaten the groundwater (depending on their mobility in the soil system) and affect terrestrial and aquatic organisms as a result of leaching from fields (9). The persistence of veterinary drugs in the terrestrial environment ranges from less than one day, to weeks or even months depending primarily on the temperature and the chemical structure of the pharmaceutical (14,17).

Still, little is known about concentrations and the fate of pharmaceuticals in solid matrices, especially sewage, sediments, and soil. This information is of great importance when evaluating the role of contaminated environmental solid samples in the spread of drugs into environment and assessing the risk of water and food contamination. Therefore, it is necessary to develop analytical methods for the quantitation of most important human and veterinary pharmaceuticals in different types of solid samples. The fate of pharmaceuticals in soil depends on either equilibrium adsorption–desorption concentrations, or on the transport phenomena associated with the type of soil (18). The mobility of the pharmaceuticals in soil, and consequently their potential for contaminating groundwaters, depends on: (*i*) the amount of drug applied; (*ii*) the intensity of the "rain" events; and (*iii*) the soil type. The tendency of pharmaceuticals to move through the soil can be well correlated with their sorption tendencies. Thus, as expected, low K_{ow} causes that analyte to be fully recovered in the leachate (for example underground waters) under the effect of rain. The adsorption of phar-

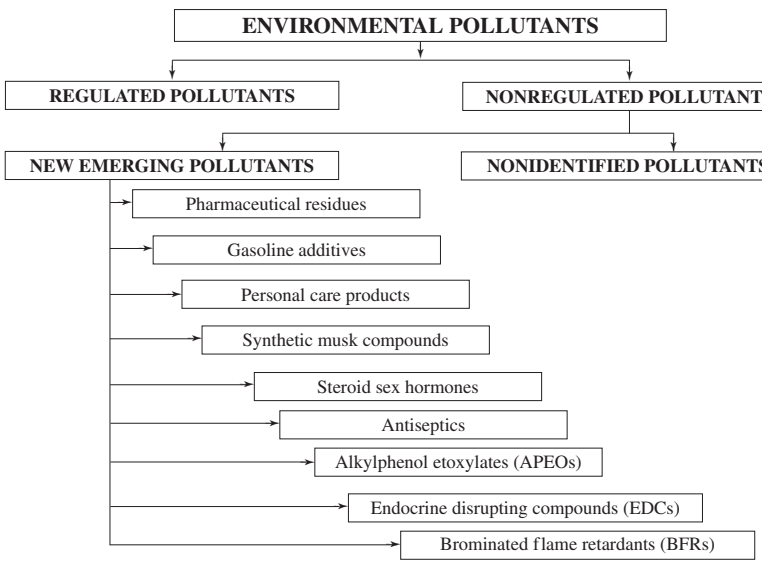

Figure 1. General classification of xenobiotics present in different elements of the environment.

Table I. Comparison of Different Extraction Samples, Solvents used for Extraction, and Clean-up Procedures

Substances	Sample matrix	Extraction procedure	Extraction solvent	Clean-up	References
Analgesics, antipyretics, anti-inflammatory	river sediments	USE	acetone–acetic acid (20/1, v/v) ethyl acetate	*SPE* **SPE cartridge:** Oasis MCX **Eluent:** methanol	(27)
	Sludge	USE	methanol acetone	*centrifuge and SPE* **SPE cartridge:** Oasis MCX **Eluent:** acetone	(2)
Antilipidemic	river sediments	USE	acetone–acetic acid (20/1, v/v) ethyl acetate	*SPE* **SPE cartridge:** Oasis MCX **Eluent:** methanol	(27)
	sludge	USE	methanol acetone	*centrifuge and SPE* **SPE cartridge:** Oasis MCX **Eluent:** acetone	(2)
Psychiatric drugs	sludge	USE	methanol acetone	*centrifuge and SPE* **SPE column:** RP-C_{18}ec **Eluent:** methanol	(2)
Oral antidiabetic drugs	sludge	USE	methanol acetone	*centrifuge and SPE* **SPE column:** RP-C18ec **Eluent:** methanol	(2)
Chemotherapeutic agents	sludge	USE	methanol–acetone	*centrifuge and SPE* **SPE column:** RP-C18ec /ENV+removal of upper RP-C18 ec layer **Eluent:** methanol	(35)
	river sediments	USE	methanol–acetone ethyl acetate	*SPE* **SPE cartridge:** Oasis MCX **Eluent:** methanol	(27)
Antibiotics					
Macrolides	river sediments	USE	methanol acetone ethyl acetate	*SPE* **SPE cartridge:** Oasis MCX **Eluent:** methanol	(36)
	agricultural soil	ASE	methanol–0.2M citric acid (50/50 v/v)	*SPE* **SPE cartridge:** SAX and HLB cartridges in tandem **Eluent:** methanol	(34)
	soil	ASE	1% (v/v) aqueous ammonia in methanol	*SPE* **SPE cartridge:** Diol SPE cartridges **Eluent:** ACN/ammonium acetate (3:2)	(28)
Sulfonamides	river sediments	USE	methanol acetone ethyl acetate	SPE **SPE cartridge:** Oasis MCX **Eluent:** methanol	(36)
	agricultural soil	ASE	methanol–0.2M citric acid (50/50 v/v)	*SPE* **SPE cartridge:** SAX and HLB cartridges in tandem **Eluent:** methanol	(34)
	animal manure	USE	ethyl acetate	*LLE* ethyl acetate	(34)
Tetracyclines	agricultural soil	ASE	methanol–0.2M citric acid (50/50 v/v)	*SPE* **SPE cartridge:** SAX and HLB cartridges in tandem **Eluent:** methanol	(29)
Metronidazole	soil	USE	methanol	centrifuge	(14)
Tylosin	soil	USE	methanol	centrifuge	(14)

maceuticals on soil with low organic carbon depends on the organic content of the matrix and the nature of the compounds.

In general sediments are less sensitive to environmental changes, such as rainfall, drought, and temperature. Therefore analysis of solid samples enables one to study long-term pollution effects, which can result in better risk assessment/management.

Occurrence and analysis of pharmaceuticals in solid samples

The actual concentrations of human and veterinary pharmaceuticals are at levels of ng/g in solid samples and often associated with complex matrices like sediments, soil, manure, etc., that makes heavy demands on the analytical work and preconcentration procedures. Another analytical challenge is the determination of drug metabolites. Many drugs are partially metabolized in the human body before excretion. The metabolites may also be harmful to the environment and it is therefore necessary to include them in the investigations.

The analysis of pharmaceuticals in solid samples has only been reported on a limited number of occasions. In the following section, several methodologies are described, showing the state-of-the-art methods for pharmaceutical analysis in solid samples. The novel analytical methods recently reported in the literature, like high-performance liquid chromatography coupled with mass spectrometry (HPLC–MS) or tandem mass spectrometry (HPLC–MS–MS) are addressed.

Sampling and storage

The quality of analytical result is only as good as the quality of the sample sent to the laboratory. There are many factors involved in choosing the proper sampling equipment for solid samples. The most important aspect of non-aqueous sampling is to assure the representativeness of the sample. An attempt must be made to maintain sample integrity by preserving its physical form and chemical composition. The proper use of appropriate sampling equipment leads to the accomplishment of these goals. Factors that contribute to the selection of soil, sediment, sludge, or manure sample include the width, depth, flow, and the bed characteristics of the area or impoundment to be sampled. A sample collected at one point in the system may be completely different from sample collected at another point. Sometimes, like in the case of manure, characteristics can also change with the seasons.

Soil can be sampled at the surface or below the surface depending on the type of information required and the kind of soil (sampling from different places) (19,20). Several samplers may be adapted for use as sediment/sludge collection devices. These include grab samplers and corers. Grabs are preferred when a high number of samples have to be collected. Box corers or multi corers are used when detailed information on the spatial distribution of analytes is required. With regards to the material used for the sampling devices, stainless steel provides the best results, except when Ni or Cr have to be monitored (9).

Collected samples are transported under cooled conditions to the laboratory and stored in the dark at *ca.* 4°C until analysis. During storage, the bacterial activity should be arrested in order to preserve the integrity of the sample. However, little attention is paid to this subject in literature. Sediment samples can be stored for up to 2 weeks in polyethylene bottles in a dark place (20).

Sample preparation

During sample preparation there are various analytical steps such as filtration, extraction, purification, hydrolysis, derivatization, and evaporation. Of the various steps in a sample preparation procedure, the extraction/purification step, which is present in almost all the analytical procedures described in the literature, is the most critical (21,22). An ideal sample preparation technique should be simple, inexpensive, efficient, selective, and compatible with various analytical techniques. It should give as high as possible recovery, supreme sample clean-up, be environmentally friendly, and should reduce amount of solvent used. In practice, it is difficult to fulfill all theses requirements. Usually the sample preparation is the most labor-intensive and very often the slowest and the most costly step in the whole analytical procedure, especially if multi-step procedures are used (23). Over the last 10 years, research into sample preparation techniques has been driven to solve these problems and find the ideal sample preparation technique. Solid samples are examples of samples, which, due to their state, cannot be directly determined. Therefore, it is necessary to extract the analytes from the matrix to the liquid phase because it permits the use of chromatographic techniques for the final determination.

Lots of factors can be considered in order to select the proper sample preparation technique (e.g., the amount of solvents used and the amount of wastes obtained, time needed for the extraction, cost and availability of instruments, cost of every operation, amount of the sample required for the extraction, automatic degree of the process, and number of steps required, which can be a source of mistakes) (24).

These extraction methods utilize a range of different extraction solvents and are generally based on mechanical shaking, ultrasonication, or Soxhlet extraction. The use of more advanced extraction techniques, such as assisted microwave extraction or accelerated solvent extraction hasn't been reported often. However, the application of novel extraction techniques to the analysis of solid samples is increasing. Alternative sample preparation techniques have various advantages over other traditional methods (shaking, ultrasonic assisted extraction, or Soxhlet), such as better reproducibility, reduced use of extraction solvent and reduced time for sample preparation. Traditional techniques like Soxhlet can take 4–48 h, with ASE or microwave assisted extraction it can achieve analyte recoveries equivalent to those obtained using traditional extraction methods in only 15 min or even less (usually less than 15 min) (25). This is because soil extractions are performed at high pressure (500–3000 psi; 1 psi = 6894.76 Pa), at elevated temperatures (50–200°C), or by using a microwave. However it doesn't change the fact that the use of alternative methods of extraction requires the optimization of lots of parameters (e.g., kind of solvent, extraction time and temperature, pressure, numbers of cycles, and flush) (26, 27).

The published literature concerning analysis of pharmaceuticals in solid matrices, including extraction processes and detection methods with LC has been recently been summarized (2).

In most methods, the next step after extraction is the clean-up

Table II. Comparison of Different Purification Detection Methods for Analyzing Pharmaceuticals in Solid Matrices, Including Extraction Processand Detection with LC–MS or LC–MS–MS

Substances	Sample matrix	LC separation		Detection method	LOD (ng/g)	References
		Column	Mobile phase			
Analgesics, antipyretics, anti-inflammatory	river sediments	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: ACN Eluent B: Mili-Q water acidifield to pH 2.9 with acetic acid	MS–MS-APCI neg. mode SRM	0.4–8	(27)
	sludge	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: ACN Eluent B: Mili-Q water acidifield to pH 2.9 with acetic acid	MS–MS-APCI neg. mode SRM	20–50	(2)
Antilipidemic	river sediments	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: ACN Eluent B: Mili-Q water acidifield to pH 2.9 with acetic acid	MS–MS-APCI neg. mode SRM	0.4–8	(27)
	sludge	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: ACN Eluent B: Mili-Q water acidifield to pH 2.9 with acetic acid	MS–MS-APCI neg. mode SRM	20–50	(2)
Psychiatric	drugs sludge	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: 5 mmol/L aqueous ammonium acetate (pH 5.7) and ACN (90:10 v/v) Eluent B: 400 mL eluent A + 600 mL ACN	MS–MS-ES pos. mode SRM	20	(2)
Oral antidiabetic drugs	sludge	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: 5mmol/L aqueous ammonium acetate (pH 5.7) and ACN (90:10 v/v) Eluent B: 400 mL eluent A + 600 mL ACN	MS–MS-ESI pos. mode SRM	20–50	(2)
	sludge	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: 5mmol/L aqueous ammonium acetate (pH 5.7) and ACN (90:10 v/v) Eluent B: 400 mL eluent A + 600 mL ACN	MS–MS-ESI pos. mode SRM	5	(35)
Chemotherapeutic agents	river sediments	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: aqueous solution of 900 mL 20 mmol/L NH3 adjusted with acetic acid to pH 5.7 Eluent B: eluent A/ACN (80/20 v/v)	MS–MS–APCI pos. mode SRM	0.4–8	(27)
Antibiotics						
Sulfonamides	river sediments	LiChrosphere RP-18ec 125 × 3 mm × 5 µm	Eluent A: aqueous solution of 900 mL 20 mmol/L NH_3 adjusted with acetic acid to pH 5.7 Eluent B: ACN (80/20)	MS–MS–APCI pos. mode SRM	0.4–8	(36)
	agriculture soils	Waters Xterra MS-C_{18} 100 mm × 2.1 mm, 3.5 µm	Eluent A: 5% methanol + 80mM formic acid Eluent B: 95% methanol + 80mM formic acid	MS–MS-ESI pos. mode MRM	5	(34)
	animal manure	Nucleosil 100-5 C_{18} 125 mm × 3 mm × 5 µm	Eluent A: ammonium acetate buffer Eluent B: ACN	MS-ESI pos. mode	100	(34)
Tetracyclines	agriculture soils	Waters Xterra MS-C_{18} 100 mm × 2.1 mm, 3.5 µm	Eluent A: 5% methanol + 80mM formic acid Eluent B: 95% methanol + 80mM formic acid	MS–MS-ESI pos. mode MRM	5	(29)
Metronidazole	soil	Hypersil BDS 250 × 2.1 mm	Eluent A: 80% ammoniumacetate (10mM) Eluent B: 20% methanol	MS-ESI pos. mode SIM	3	(14)
Tylosin	soil	Hypersil BDS 250 × 2.1 mm	Eluent A: 80% ammoniumacetate (10mM) Eluent B: 20% methanol	MS-ESI pos. mode SIM	7	(14)

and purification of samples. Clean-up of extracts, when performed, has been carried out by solid phase extraction (SPE), liquid–liquid extraction (LLE), gel permeation chromatography (GPC), and semi-preparative HPLC. SPE has been preferred in most instances because it is fast, requires low volume of organic solvents, presents low contamination risk and can be used on-line. SPE clean-up of extracts has always been performed with reversed-phase adsorbents. The main mechanism of SPE is to retain the pharmaceuticals onto the cartridge and to extract them efficiently using appropriate solvents. Thus, selecting the most suitable cartridge with respect to the polarity of analytes, sample matrix, or solution is important. Reversed-phase SPE is normally used with a polar or moderately polar sample matrix and hydrophobic interaction is involved between the carbon-hydrogen bond in the analytes and the functional groups on the silica surface of the cartridge. Ion-exchange SPE for both cation-exchange and anion-exchange SPE is used with charged compounds in solution. The main retention mechanism of ion-exchange SPE is electrostatic attraction of the charged functional groups of compounds to the functional groups of the changed silica surface in the cartridge (2).

Several different cartridges [e.g., Lichrolute EN, C_{18}, HLB (hydrophilic–lipophilic balanced), and diol SPE] have been used to clean up or purify the pre-extractants in solid matrices and to extract pharmaceutical compounds in WWTPs, surface water, and groundwater (28–33). HLB cartridges are widely used due to the broad range of pH that they can tolerate. Moreover, no significant interference or irreversible binding can occur with silica-based cartridges. Furthermore, tandem-SPE methods (strong anion exchange SAX + HLB) have been used to remove humic material with SAX and to retain antibacterial agents with the HLB cartridge in surface water and agricultural soil (30,34).

A comparison of different extraction techniques and solvents used for the extraction and clean-up procedures enabling purification of extracts of pharmaceutical compounds in solid samples is presented in Table I.

Separation and detection

The analytical methodology for the determination of pharmaceuticals in complex environmental matrices is still evolving, and the number of methods described in the literature has grown considerably. The two primary techniques to separate and detect pharmaceuticals in environmental matrices at low concentrations are gas chromatography (GC) and liquid chromatography (LC) combined with UV, MS, or even MS–MS. GC–MS was used to measure eight pharmaceuticals and their metabolites in a wetland (39) as well as to track the occurrence, fate, and removal of over 80 pharmaceuticals in the nine different categories in the aquatic environment (40). However, for many of today's polar drugs, GC–MS analysis is hampered by difficult derivatization protocols. HPLC coupled with UV (DAD) or MS detector is ideally suited for these polar compounds. The UV–DAD detector presents some disadvantages over MS, because UV is not sufficiently sensitive and selective. However, MS allows for identification of pharmaceuticals and degradation. Furthermore, the UV analysis methods require long run times to minimize the potential for coelution. In recent decades, LC–MS and LC–tandem MS have experienced an impressive progress, both in terms of technology development and application (41).

Detailed, comprehensive reviews of LC–MS analysis are available, covering a range of emerging contaminants, related pollutants, micro-organisms. and humic acids (42,43).

Among LC modes (e.g., reversed-phase, ion-exchange, and size-exclusion), reversed-phase with octadecyl (C_{18})-bonded or octyl (C_8)-bonded silica packing is the stationary phase most commonly used for pharmaceutical analysis. Ion-exchange and size-exclusion methods are used to separate ionic compounds and molecules respectively, on the basis of their molecular weight. Few studies have been reported on ion-exchange and size-exclusion methods due to the high concentration of salt in the mobile phase challenging equipment reliability. An ion-exchange chromatography with a polymeric column and acidic eluent has been applied to measure tetracycline residual in milk and the rate of removal of oxytetracycline in a biochemical technology WWTPs process (44).

The composition of the mobile phase is an important factor for improving separation in LC. An acidic condition with acetonitrile–water and methanol–water mixtures with gradient elution is among the most common approach for improved peak shape in chromatography. Non-volatile additives, such as oxalic acid, should be avoided in case MS is applied.

Nowadays, applications of LC technique combined with a variety of MS spectrometers (in meaning of different ionization sources and mass analyzers) have been widely reported with the respect of pharmaceutical residuals in the environment (2,45–53).

In sediments, most of the data on drug residues data found in the literature concerns the occurrence of estrogens and antibiotics. Given the relatively low polarity, in particular for estrogens with K_{OW} 2.5–5, sorption to sediments appears quite likely to be cumulative process. Steroidal hormones typically reported in the literature are 17 α-ethinyl estradiol, diethylstilbestrol and diethylstilbestrol acetate. All of them have been identified at low ng/kg level (1). Some antibiotics, because of their elevated lipophilicity, have already been found in sediments. Antibiotics like ofloxacin, chlortetracycline, flumequine, and oxytetracycline have also been detected at low-medium µg/kg (1,49). The detection of tetracyclines in sewage sludge or sediments is also documented (54,55).

The science of environmental analytical chemistry has been-driven to look forever-smaller quantities of pharmaceuticals in the environment, at the level of a few nanograms per litter. It seems that without development of the capability of LC–MS, it would be not possible to detect many harmful compounds at the levels at which they have a biological effect in the environment. A new generation of LC–MS instruments was developed, LC–MS–MS. LC–MS–MS techniques, such as triple quadrupoles (QqQs) and ion traps, are in common use. More recent approaches in LC–MS–MS are linear traps (LITs), new generation QqQs and hybrid instruments, quadrupole-time of flight (Qq-TOF), and linear traps (Qq-LITs), which are gaining widespread acceptance in several application areas (54).

The most widely used LC–MS–MS methods add additional collision energy to fragment protonated or deprotonated ions that are formed in the ionization source. The additional fragmentation step may require more analysis time, but it enhances the

selectivity of the complex-matrix sample by avoiding co-elution of analytes and interferences in samples compared to LC–MS with single quadrupole (2,24).

Table II summarizes the most recently published literature for purification and detection methods for analyzing pharmaceuticals in solid matrices, including the extraction process and detection with LC–MS or LC–MS–MS.

Conclusions

Veterinary and human pharmaceuticals are being used constantly with little information on their fate and effect in the environment. But recently there is more pressure to take care of the environment and manage the risk posed by pharmaceuticals. At present, an important step in the development of new pharmaceuticals is not only to achieve the best therapeutic effect but estimate the real cost and benefits of the production of new drugs. The risk to the environment and the indirect effects on people and animals due to environmental contamination, need to be assessed to be able to decide whether the benefits exceed the costs. This review has covered the existing information on recent developments of analysis methodsof pharmaceuticals in solid samples, comparing the results obtained for analysis of drugs with different extraction methods and advanced detection techniques. Knowledge regarding the environmental occurrence of pharmaceutical products is increasing, but information in the peer-reviewed literature regarding extraction, detection and the fate and effects of most pharmaceuticals is limited.

The monitoring of drugs in solid environmental samples normally requires the use of time- and labor-consuming methodologies. The quality assurance of each step involved in the whole analytical procedure, including sampling and storage, is essential for the reliability of the analytical determinations. A big challenge for analytical chemistry is the optimization of each step and to find the best compromise in terms of recovery for all the compounds of interested.

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