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Review

Detection and quantification of residues and metabolites of medicinal products in environmental compartments, food commodities and workplaces. A review

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ABSTRACT

The toxicological assessment of medicinal products (MPs) and their residues and metabolites in the environment have become a challenging task worldwide. The contamination of environmental compartments, biota, workplace, foodstuff and feedstuff by residues and metabolites of these substances poses a risk to human health which is still far from being fully understood. On the other hand, existing analytical methods not always possess sufficient detection power to quantify residues of MPs at very low concentrations. This review sets forth some of the most significant contributions made in this field over the past decade with a special focus on novel fit-for-purpose analytical approaches for the detection, identification and quantification of these pollutants and the assessment of their noxious potential for human beings and the environment.

Contents

Abbreviations: AMX, amoxicillin; AOZ, 3-amino-2-oxazolidinone; APCI, atmospheric pressure chemical ionization; ASV, anodic stripping voltammetry; BCF, bioconcentration factor; BI, bead injection; CE, capillary electrophoresis; CID, collision induced dissociation; CFUF, cross-flow ultrafiltration; CV, cyclic voltammetry; CZE, capillary zone electrophoresis; DAD, diode array detector; DP(s), degradation product(s); ED(s), endocrine disruptor(s); EIC(s), environmental introduction concentration(s); EIS, electrochemical impedance spectroscopy; ELISA, enzyme-linked immuno sorbent assay; EPI, enhanced product ion; ERA, environmental risk assessment; ESI, electrospray ionization; FD, fluorescence detection; FI, flow-injection; FPIA, fluorescence polarization immunoassay; FT, Fourier transform; GC, gas chromatography; GC×GC, two-dimensional GC; HILC, hydrophilic interaction liquid chromatography; HPLC, high performance liquid chromatography; HPTLC, high performance thin layer chromatography; HR, high resolution; HRA, health risk assessment; IDA, information dependent acquisition; IT, ion trap; LC, liquid chromatography; LIF, laser-induced fluorescence; LIT, linear ion trap; LLE, liquid–liquid extraction; LoD(s), limit(s) of detection; LoQ(s), limit(s) of quantification; LOV, lab-on-valve; MDe, micellar desorption; MDi, membrane distillation; MEEKC, microemulsion electrokinetic chromatography; MEPS, microextraction packed sorbent; MIT(s), microbial inhibition test(s); MP(s), medicinal product(s); MRL(s), maximum residue limit(s); MRM, multiple reaction monitoring; MSPD, matrix solid-phase dispersion; MSy, multisyringe; MS/MS, tandem mass spectrometry; NAT, Nouws antibiotic test; NET, norethindrone; NMR, nuclear magnetic resonance; NSAID(s), non-steroidal anti-inflammatory drug(s); PCP(s), personal care product(s); PLE, pressurized liquid extraction; POCIS, polar organic chemical integrative sampling; PT(s), proficiency test(s); PTV, programmed temperature vaporizer; Q, quadrupole; QA, quality assurance; QC, quality control; QuEChERS, quick, easy, cheap, effective, rugged and safe; QQQ, triple quadrupole; RM(s), reference material(s); RP, reversed phase; RSD, relative standard deviation; SIM, selected ion monitoring; SPE, solid phase extraction; SPM, suspended particulate matter; SPME, solid phase micro-extraction; SRM, selected reaction monitoring; STP(s), sewage treatment plant(s); SWV, square wave voltammetry; TAT, total antibiotics test; TFME, thin film microextraction; TLC, thin layer chromatography; ToF, time-of-flight; UV, ultraviolet; UPLC, ultra-high performance liquid chromatography; WTP(s), wastewater treatment plant(s).

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1. Introduction

The presence of residues and metabolites of medicinal products (MPs) in environmental media, biota, food and workplace poses nowadays a serious threat to human health and environmental integrity. This challenge is ever more attracting the attention of the international scientific community, the decision makers and the layman and concern has been expressed over the past few years over the deleterious consequences of the discharge of MPs, often as unused or expired products, into various environmental compartments, to say nothing of their occurrence in foodstuff and feedstuff and of their undue presence in the workplace [1–3]. The growing concern about residues of MPs as contaminants stems from their physical and chemical behavior resembling that of other persistent xenobiotics with potentially adverse effects.

When MPs are released to the environment, often as a consequence of domestic use, they spread over different compartments and undergo transformation primarily on the basis of their chemical structure as well as of the nature of the host compartment. Residues of various types of MPs (*e.g.*, antitumoral agents, antibiotics, antidepressants and hormones) have been actually detected in various environmental compartments, such as natural waters, soils, sediments, air and biota. Such widespread occurrence obviously raises a number of questions among which the reliable quantification of the concentrations of MPs in the various media is of prime importance to evaluate whether they can pose an appreciable risk to exposed biota and human beings.

The striking advancement made by medicine in recent decades has had undeniable benefits for the society as a whole, primarily because of the widespread availability of MPs in the medical practice to effectively treat most pathologies. On the other hand, the toll paid is basically due to the still limited understanding of the effects of the discharge of such substances into the environment independent of whether this is the consequence of the proper use of MPs or because of fortuitous contamination processes.

The key facets of this subject have been already covered in quite a number of recent surveys (see, *e.g.*, [4–23]). In turn, this review deals in particular with the most promising analytical and–to a lesser extent – bioanalytical approaches developed so far to quantify such contaminants in waters, soils and sediments, biota, foodstuff, feedstuff and workplace and an attempt is also made to outline possible future trends. The relevant literature has been scanned mostly over the past ten years and the records deemed to be particularly representative are grouped in the below thematic sections with no claim of exhaustiveness, but rather with the only intention of providing the interested reader with some examples of the wealth of information available in this field.

2. Water

2.1. Drinking water

A method based on solid phase extraction (SPE) coupled to ultra-high performance liquid chromatography (UPLC)–tandem mass spectrometry (MS/MS) to quantify residues of MPs at the ng/L level was devised [24]. The method was applied to the determination of a number of analytes including cardiovascular, veterinary and human antibiotics, neuroleptics, non-steroidal anti-inflammatory drugs (NSAIDs) and hormones in drinking water from some treatment plants in western France. Matrix effects were carefully assessed.

Nitrofurans (nitrofurazone, nitrofurantoin, furazolidone, furaltadone), nitroimidazoles (metronidazole, ronidazole, dimetridazole) and chloramphenicol were simultaneously quantified in feed water by a SPE-high performance liquid chromatography (HPLC)–ion trap (IT) electrospray ionization (ESI)-tandem MS/MS [25]. Matrix effects were prevented by using isotope-labeled internal standards. The SPE step resorted to an Oasis HLB cartridge (400 enrichment factor). The aforementioned antimicrobial agents could be eluted in 18 min using a gradient acetonitrile – acidified water (pH 5.0) elution. Acceptable precision (3.4–26.6%), good linearity (R^2 = 0.979–0.999) and satisfactory recovery rate (88.4–110.1%) characterized the method along with excellent limits of detection (LoDs) and limits of quantification (LoQs), *i.e.*, 0.002–0.06 μg/L and 0.005–0.25 μg/L, respectively. This analytical system proved of practical value to monitor residues of MPs in feed water.

The LoDs afforded by modern analytical techniques for quantifying trace MPs in drinking water were reviewed by Kuhlmann [26]. The occurrence of pollutants such as X-ray contrast agents, anti-epileptics, lipid sinks, antibiotics, β-blockers and sedatives in the River Rhine was also discussed.

Residues of MPs belonging to various therapeutic classes such as cardiovascular, veterinary and human antibiotics, neuroleptics, NSAIDs, hormones and other miscellaneous pharmaceutical compounds were quantified in drinking water by SPE followed by UPLC coupled to MS/MS [27]. Samples were taken at various drinking water treatment plants in the west of France and concentrations in the low ng/L range could be measured. The performance of the standard addition method was compared with that of conventional external calibration with internal standard correction.

Venlafaxine and bupropion were detected at very low concentrations (less than 0.005 mg/L) in untreated drinking water, whereas they were below the LoDs in treated drinking water [28].

2.2. Surface water

Hundred thousand tons of MPs are thought to be used yearly in human and veterinary medicine, to say nothing of the amounts necessary for livestock and aquaculture. After administration, their residues and transformation substances can to some extent enter environmental media as they are not completely retained in wastewater treatment plants. This leads to high concentrations of these contaminants in surface water, especially so in the case of developed countries. Unluckily, reliable experimental information on their levels in aquatic biota, mechanisms of partitioning to biosolids, soils, and sediments and bioaccumulation properties is often rather poor.