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Pharmaceutical substances in ambient particulates: A preliminary assessment

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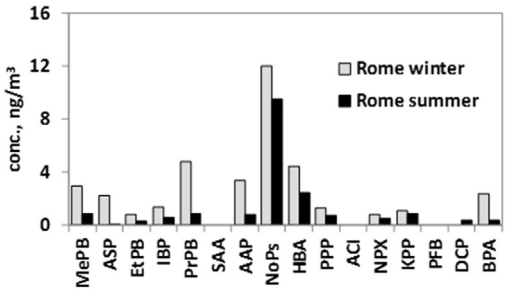
HIGHLIGHTS

- Pharmaceutical compounds (PCs) were investigated for the first time in airborne particulates.
- PCs were silylated with MTBSTFA and analyzed by cold on-column injection and GC-MSD.
- PCs could be characterized in most examined samples.
- Individual PC contents in particulates ranged <0.1–8.6 ng m^{-3}, depending on city and year season.

GRAPHICAL ABSTRACT



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ABSTRACT

Till now, no attention has been paid to pharmaceuticals (PCs) in the air, though they are known to affect waters, soils, foods and biota. This paper describes the first attempt to characterize the PC occurrence in the air. Airborne particulates (PM_{10} or $PM_{2.5}$ fractions, from Amsterdam, Netherland, Rome and Rende, Italy) were sampled on quartz fiber filter by means of pumping systems operating at medium-volume conditions (16 or 38.5 L min^{-1}). The samples were solvent extracted through sonication with a dichloromethane:acetone:methanol mixture and reduced close to dryness; three fractions of the residue were separated through column chromatography; they comprised non polar, low polar and very polar organic compounds, respectively, and PCs were in the third one. Chemical analysis was performed by means of gas chromatography coupled with mass spectrometric detection (GC-MSD), after treatment of solutions with methyl,tertzbutylsilyl-trifluoroacetamide (MTBSTFA) to form silyl derivatives of most PCs. The following substances were investigated: acetaminophenol, ibuprofen, ketoprofen, fenoprefen, naproxen, fenofibrate, diclofenac, acetylcysteine and sulfanilamide; *p*-hydroxybenzoic acid and salicylic acid; and parabens (methyl, ethyl and propyl). Except aspirin, acetamidophenol, acetylcysteine and sulfanilamide, the target compounds could be quantified with good repeatability, reproducibility and percent recoveries (on the average, ~7.5%, ~7.1% and 91%, respectively). The PC concentrations ranged <0.1–8.6 ng m^{-3}; season dependent drug profiles could be observed in Rome and Rende.

1. Introduction

Pharmaceuticals (PCs) are gaining more and more attention as environmental contaminants, due to occurrence in water matrices of both active principles and metabolites/by-products (Sarmah

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et al., 2006; Jindal, 2012). A number of analytical methods have been optimized to characterize PCs in different media (Buchberger, 2011; Omar et al., 2016); methods are overall based on (ultra) high pressure liquid chromatography coupled with mass spectrometric (Vanderford and Snyder, 2006; Petrovic et al., 2006; Ferrer and Thurman, 2012; Gracia-Lor et al., 2011; Grabic et al., 2012), fluorescence (Patrolecco et al., 2013), diode-array (Vera-Candioti et al., 2008) or electrochemical (Martinez et al., 2012) detection, operated after enrichment and clean up obtained from column chromatography, solid phase extraction or micro extraction (Castiglioni et al., 2005; Tong et al., 2009; Gurke et al., 2015). Other procedures apply capillary electrophoresis (Ahrer et al., 2001; Macia et al., 2004), gas chromatography (Gatidou et al., 2007; Möder et al., 2007) and/or drug derivatization into easier processed analytes. Nowadays, contamination of wastes (Ternes, 1998; Kolpin et al., 2002; Sebok et al., 2008; Subedi et al., 2013; Verlicchi and Zambello, 2015), river, lake and offshore waters (Kolpin et al., 2002; Boyd et al., 2003; Benotti et al., 2009; Fernandez et al., 2010; Bu et al., 2013; Nikiforos et al., 2016; Thomaidis, 2016) is ascertained, and measurements have been carried out for clinical and preventive medicine purposes; PCs have been also monitored in animals and biota (Ollilainen et al., 2001; Brooks et al., 2005; Subedi et al., 2012). Other studies focused on the fate of PCs after release into the environment (Richardson and Bowron, 1985; Hörsing et al., 2011; Boix et al., 2016) and effectiveness of removal practices (Castiglioni et al., 2006; Petrovic et al., 2009; Gros et al., 2010), as well as the exposure and possible threat for humans (Schwab et al., 2005; Pomati et al., 2006; EMEA, 2006, 2010; Bruce et al., 2010; Ågerstrand et al., 2015) and animals (VICH, 2005; Kim et al., 2007; Brausch et al., 2012). Finally, PCs have attracted the attention of legislators, which established rules and limits to their use and disposal (WHO, 2011, 2012; USEPA, 2002, 2010). Fourteen major categories of pharmaceuticals exist, namely concerning: A) gastro-intestinal apparatus and metabolism; B) blood and blood forming organs; C) cardiovascular system; D) skin; G) genitourinary system, sex hormones; H) hormones (systemic and insulin, except sex hormones); J) Infections (anti-infectious for systemic use); L) antineoplastic and immune-modulating agents; M) musculoskeletal system; N) nervous system; P) parasite killers, insecticides, repellents; R) respiratory system; S) sensory organs; and V) various. Anyway, investigations are overall focused on the most used chemicals or the most loading on National Health Systems.

By contrast, PCs have not been yet investigated in the air (as gaseous or particulate), nor in surface and soil dust, both outdoors and indoors. Since PCs are taken as such or as food contaminants/additives, they are expected to not occur at all in the air, or eventually occur at very low extents as metabolites. Despite that, whereas verified the occurrence of PCs both in suspended particulates and house dust would be of environmental concern, due to potential threat for humans it deserves; in fact, the presence of psychotropic substances, some of which are used for recreational or pharmacological purposes, has been demonstrated in air (McKenzie et al., 2013; Cecinato et al., 2014; Mastroianni et al., 2015). Besides, suitable information would be drawn from detecting PCs either in the form of native substances, metabolites or decomposition by-products. In fact, the PC presence would depend on direct dispersion into the environment (e.g., as a consequence of over-dosage, wasting, use by date, and improper consumption) or on release by humans and animals; besides, their chemical form in the air would depend on the persistence of substances in the environment. The goal of our investigation was to establish the occurrence of PCs in the atmosphere; since most PCs are polar organics, attention was paid to fine fraction of airborne particulates, which is known to hold most of organic contaminants like *n*-alkanes and PAHs. In the lack of any preliminary data about atmospheric PCs, our focus was primarily on the most used substances in Italy and Europe as well as on chemicals used as additives and anti-oxidants in cleaning and health care products. This study was necessarily limited; in fact, it was conceived as a first step of further investigations extended to gas phase and new categories of pharmaceuticals (e.g., antibiotics), as well to metabolites and degradation products. Besides, it would be of concern to understand if pharmaceuticals are preferably associated to fine and ultrafine particles or to settled dusts; that could have consequences on the possible health impact of atmospheric PCs.

2. Materials and methods

Solvents (*n*-heptane, *n*-hexane, dichloromethane, chloroform, acetonitrile, acetone and methanol), all of residue analysis or far UV HPLC grade purity (ROMIL, Waterbeach, Cambridge, UK), were purchased from Delchimica Glassware, Naples, Italy. Pharmaceutical standards were provided by Chemical Research, Rome, Italy, and individually dissolved in acetonitrile at concentration level of ≈2 mg/mL; calibration standard mixtures (0.02–2.0 μg/mL) were obtained through dilution with chloroform. The silylating agent *N*-methyl-*N*-(tert-butyldimethylsilyl)trifluoroacetamide MTBSTFA (+1% tert-butyldimethylchlorosilane) was purchased from Sigma, Milan, Italy.

The substances investigated were:

- ibuprofen [IBP], ketoprofen [KPP], fenoprofen [PPP], naproxen [NPX] (anti-inflammatory drugs), aspirin [ASP], acetaminophenol [AAP], salicylic acid [SA] (analgesics, antipyretics), fenofibrate [FFB] (anti-hypercholesterolemia), diclofenac [DCP] (anti-rheumatic, anti-inflammatory), furosemide [FUS] (diuretics), acetylcysteine [ACY] (mucolytic, nephroprotective, anti-hemorrhagic) and sulfanilamide [SAA] (antibiotic, antibacterial);
- parabens (methyl [MePB], ethyl [EtPB] and propyl [PrPB]); *p*-hydroxybenzoic acid [HBA] (anti-bacterial compounds).

Caffeine, often regarded as pharmaceutical was not taken in account in this study, due to its wide consumption in beverages (tea, coffee). Chemical formulas of all of them except sulfanilamide comprised OH or COOH groups, which were converted into silyl ethers before instrumental analysis; the corresponding derivative products were free of interferences and easily eluted during GC runs.

2.1. Procedure of analysis

The analytical procedure (see Fig. 1) was adapted from those optimized for characterizing psychotropic substances and PAHs, described elsewhere (Cecinato et al., 2014; Romagnoli et al., 2014). Sample amounts corresponding to 170–450 m^3 of air were examined. The samples were spiked with *n*-heptandioic acid (DCA7) and diphenyl acid (DPA), chosen as reference compounds for analysis, and extracted through ultra-sonic bath (22 min, three times) with 12 mL of a dichloromethane, acetone and methanol mixture (DAM, 50:30:20 in volume). The extracts were passed through a PTFE filter (porosity = 0.45 μm) and reduced close to dryness under ultra-pure nitrogen. The residue was back dissolved with small aliquots of isooctane (0.25–0.40 mL, four times) and transferred to the top of a silica gel mini-column (1.0 g, i.d. = 6 mm, deactivated with 2.0% of water). The first fraction eluted with *n*-heptane (5 mL) comprised *n*-alkanes and non-polar compounds; then, a dichloromethane/*n*-hexane mixture (20:80, 5 mL) allowed to collect low polar compounds including PAHs; finally, the DAM mixture (6 mL) eluted PCs and polar organics including alcohols, phthalates and acids. After solvent change to acetonitrile, the 3rd fraction was treated with MTBSTFA (65 °C, 40 min) in a screw-capped vial, reduced to dryness