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Analysis, occurrence, fate and risks of proton pump inhibitors, their metabolites and transformation products in aquatic environment: A review

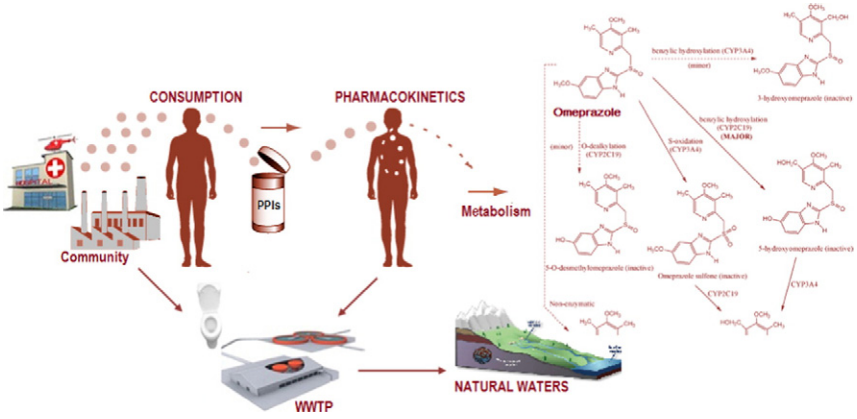
Christina I. Kosma [a], Dimitra A. Lambropoulou [b,*], Triantafyllos A. Albanis [a]

[a] Department of Chemistry, University of Ioannina, Ioannina, 45110, Greece
[b] Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

HIGHLIGHTS

- Occurrence and fate of PPIs and their metabolites/TPs in the aquatic environment
- Overview of the analytical methods applied, using LC-MS techniques
- Omeprazole attended the most frequent analysis
- Determination and behavior of omeprazole's metabolites/TPs in the environment
- More ecotoxicological research is needed to assess the risks of PPIs.

GRAPHICAL ABSTRACT



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ABSTRACT

Proton pump inhibitors (PPIs) which include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, are extensively used for the relief of gastro-intestinal disorders. Despite their high worldwide consumption, PPIs are extensively metabolized in human bodies and therefore are not regularly detected in monitoring studies. Very recently, however, it has been shown that some omeprazole metabolites may enter and are likely to persist in aquatic environment. Hence, to fully assess the environmental exposures and risks associated with PPIs, it is important to better understand and evaluate the fate and behavior not only of the parent compound but also of their metabolites and their transformation products arising from biotic and abiotic processes (hydrolysis, photodegradation, biodegradation etc.) in the environment. In this light, the purpose of this review is to summarize the present state of knowledge on the introduction and behavior of these chemicals in natural and engineering systems and highlight research needs and gaps. It draws attention to their transformation, the increase contamination by their metabolites/TPs in different environmental matrices and their potential adverse effects in the environment. Furthermore, existing research on analytical developments with respect to sample treatment, separation and detection of PPIs and their metabolites/TPs is provided.

* Corresponding author.
E-mail address: dlambro@chem.auth.gr (D.A. Lambropoulou).

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1. Introduction

Proton pump inhibitors (PPIs) or gastric acid pump inhibitors are among the most commonly used drugs worldwide and are used for the treatment of gastro-intestinal disorders (such as dyspepsia, peptic ulcer, *Helicobacter pylori* infection, gastroesophageal reflux disease, gastrointestinal complications and Zollinger-Ellison syndrome) where reduction of gastric acid secretion is beneficial (Pilbrant, 1993; Roche, 2006; Shi and Klotz, 2008). Omeprazole was the first proton pump inhibitor which was introduced in the market in 1989, and next lansoprazole (1995), pantoprazole (1997), rabeprazole (1999) and esomeprazole (pure *S*-isomer of omeprazole) (2001) became available (Shi and Klotz, 2008). All PPIs contain a 2-pyridylmethylsulfinylbenzimidazole pharmacophore (Table 1) and differ only in the nature of substituents on the pyridine and benzimidazole rings (Addo et al., 2014).

PPIs produce a long-lasting and potent non-reversible inhibition of the gastric proton pump H+/K + ATPase in paretal cells (Guo et al., 2011; Horn, 2000; Olbe et al., 2003). They bind strongly to serum proteins and are extensively metabolized by CYP450 family of enzymes. In addition, CYP2C19 isoform is particularly important and influences the pharmacokinetics, pharmacodynamics and clinical outcome of PPIs (Horn, 2000; Roche, 2006; Shi and Klotz, 2008).

Since, PPIs are extensively metabolized in human bodies (Li et al., 2004; Shi and Klotz, 2008), it seems that they have a low potential to reach the environment at large amounts. In this sense, the occurrence of PPIs in aquatic environment can be attributed to human metabolism as well to various degradative/transformative processes (hydrolysis, photodegradation, biodegradation etc.) that take place in different environmental compartments. This statement is supported by recent attempts (Boix et al., 2013, 2014; Kosma et al., 2014b) to correlate their use with the concentration detected in the aquatic environment, in which the parent compounds of PPIs are scarcely detected. For example, low concentrations of omeprazole were detected in urban and hospital WWTPs as well as in surface and river waters (Gómez et al., 2007; Kosma et al., 2014b; Pedrouzo et al., 2008; Valcárcel et al., 2011). Although, PPIs are not regularly detected, considering their high use (Godman et al., 2009, 2011; Woldegiorgis et al., 2009) its analytical monitoring becomes relevant. In addition, in view of the recent reports dealing with the detection of many metabolites and environmental Transformation Products (TPs) in aqueous samples (Boix et al., 2013, 2014, 2016; Boleda et al., 2013; Hernández et al., 2011; Gracia-Lor et al., 2014; Ibáñez et al., 2016; López et al., 2014; Ibáñez et al., 2016), environmental contamination by PPIs should be checked and evaluated more thoroughly.

In this regard, the aim of this article is to provide an overview of the current state of knowledge on: a) the transformation mechanisms and pathways that contribute to the input of PPIs in the aquatic environment, b) the analysis and occurrence of their metabolites/TPs in WWTP influents and effluents and receiving surface waters c) the application of advanced treatment processes such as advanced oxidation processes (AOPs) in the degradation of PPIs and d) the potential hazards associated with the occurrence and persistence of PPIs in the environment. From analytical point of view, we set out the analytical methods applied, using liquid chromatography mass spectrometry (LC-MS) techniques, focusing on their capabilities and potentials concerning their application for identifying the unknown contaminants (metabolites and/or TPs) in environmental matrices. We state examples of applications and when it is possible we try to give future points that have not been totally investigated yet. Under this aspect, over the past few years a growing number of articles have been published and are presented in Fig. 1.

2. Consumption of PPIs

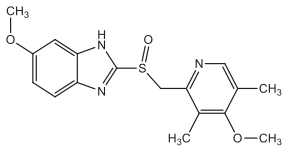
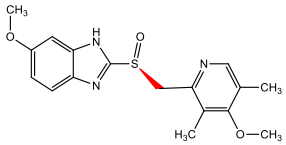
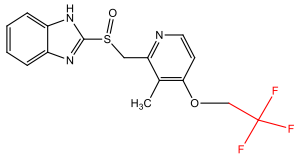
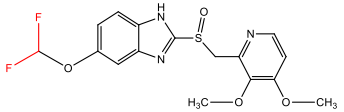
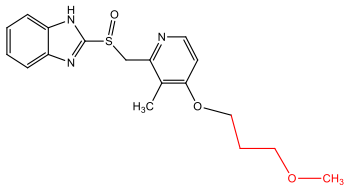
Recent studies have reported the increment of PPIs utilization and consumption, in European countries year by year (Godman et al., 2009, 2011; Woldegiorgis et al., 2009). In particular, Godman et al. (2009), captured utilization of dispensed prescriptions of PPIs in ambulatory care from 2001 to 2007, using defined daily doses (DDD) as well as DDDs/1000 inhabitants/day (DDD/TID) for patients covered by the social health insurance system, in Austria. According to the results, since generics of omeprazole and lansoprazole became available in 2003, there was an increase in prescribing of both products. By 2007, 89.5% of omeprazole dispensed on a DDD basis was generic omeprazole, while it was lower for lansoprazole (65.2%). This fact was helped by larger package sizes of these PPIs, as well as higher strength of generic omeprazole (40 mg) becoming available without prior approval (Godman et al., 2009). In another recent study, Godman et al. (2011), studied the utilization (DDDs) and expenditure (Euros and local currency) of PPIs in 19 European countries and regions from 2001 to 2007. These were Austria, Croatia, Estonia, France, Finland, Germany, Italy, Lithuania, Norway, Portugal, Poland, Republic of Ireland, Serbia, Slovenia, Spain, Sweden, Turkey, and the United Kingdom. The results showed that in both Lithuania and Poland, there was approximately a twofold difference in the rate of increase in utilization (DDD basis) versus the rate of increase in reimbursed expenditure of the PPIs between 2001 and 2007. For instance, Lithuania utilization increased 10.8 fold between 2001 and 2007 and Poland over 150 fold between 2002 and 2007. This appreciable increase in utilization, was considerably greater than in the other European countries. General findings from the study, showed more limited utilization of the PPIs among Central and Eastern European countries compared with Western European countries (Godman et al., 2011). Furthermore, Woldegiorgis et al. (2009), reported that omeprazole and esomeprazole belong to the top-40 selling drugs in Nordic countries during 1997–2007. In all Nordic countries, omeprazole is the major PPI substance on the markets. In November 2000 the enantiopure version of omeprazol, esomeprazole, was granted market admission and from 2001 there is sales statistics also for esomeprazole. In most countries one can observe a decline in the sales of omeprazole accompanying the rapid sales increase of esomeprazole in the years 2001–2003. Nevertheless for both compounds sales in Sweden have increased by 63% (from 1 tonne in 1997 to approximately 2.5 tonnes in 2007). In Denmark, and Norway the consumption has increased in a similar fashion (74–77%), while the sales increase in Finland and Iceland in amounts of 89–90%, respectively (Woldegiorgis et al., 2009). Finally, Ortiz de García et al. (2013), estimated the consumption of PPIs sold taking into account the number of packages commercialized in 2009, and the results showed that the consumption of omeprazole, pantoprazole, lansoprazole and esomeprazole was 13,850–27,710, 3410–6820, 2020 and 806–3226 kg/year, respectively.

3. Sources and pathways of PPIs in the environment

Since after administration, PPIs are extensively metabolized in the human body (Li et al., 2004; Shi and Klotz, 2008), little if any unchanged drug was excreted into the effluent and reach the wastewater treatment plant (WWTP). Looking at all compounds, approx. 70–95% of the consumed amount of PPIs is excreted as inactive or pharmaceutically active metabolites (e.g hydroxyl-omeprazole, hydroxy-lansoprazole, desmethyl-pantoprazole) in urine and feces (Fig. 2). For example in the case of omeprazole, the majority of the dose (about 77%) was eliminated in urine whereas the remainder of the dose was recoverable in feces, implying a significant biliary excretion of the metabolites of omeprazole (Andersson et al., 1993). At least six metabolites were identified in urine, from which two were identified as hydroxyomeprazole and the corresponding carboxylic acid (Petsalo et al., 2008). Three metabolites have been identified in plasma, the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole (Espinosa Bosch et al., 2007; Song and Naidong, 2006).

PPIs and their metabolites are only partially eliminated in WWTPs (Rosal et al., 2010). If they are not eliminated during the purification process, they pass through the sewage system and may end up in the

Table 1
Physicochemical properties of the proton pump inhibitors.

Compounds	Structural formula	Molecular formula	MW	pKa	LogKow	Koc (L/Kg)	Henry's law constant (atm m^3 mol^{-1})	Kd (L/Kg)	Sw (mg/L) (25 °C)	Excretion (%)
Omeprazole (OME)		$C_{17}H_{19}N_3O_3S$	345.42	4[a]/8.8[a]	2.35[b]/3.4[c]/1.4–2.4[d]	871.3[h]	3.0E−19[h]	–	82.28[c]/130[e]	<1[k]/5[d]/30[l]
Esomeprazole (ESO)		$C_{17}H_{19}N_3O_3S$	345.417	4[e]/8.8[e]	3.40[f]	–	–	48[e]	340[e]	20[l]
Lansoprazole (LANSO)		$C_{16}H_{14}F_3N_3O_2S$	369.363	3.83[g]/8.5[b]/8.73[d]	2.38[b]/1.73[d]	4856[b]	–	–	250[f]	5[d]
Pantoprazole (PANTO)		$C_{16}H_{15}F_2N_3O_4S$	383.371	3.92[h]/8.19[h]	2.2[f]	–	–	–	495[i]	<1[k]/20[l]
Rabeprazole (RABE)		$C_{18}H_{21}N_3O_3S$	359.444	4.4[j]/5.0[n]/8.5[j]	1.17[f]	–	–	–	336[i]	<1[m]

[a] Gómez et al. (2007).
[b] Thomas et al. (2010).
[c] Verlicchi et al. (2012).
[d] Hernando et al. (2007).
[e] Holm (2007).
[f] Estimated from pubchem.
[g] Roche (2006).
[h] Domènech et al. (2011).
[i] Predicted properties from drugbank.
[j] Van De Steene and Lambert (2011).
[k] Besse et al. (2008).
[l] Ortiz de García et al. (2013).
[m] Lu et al. (2015).
[n] Pace et al. (2007).

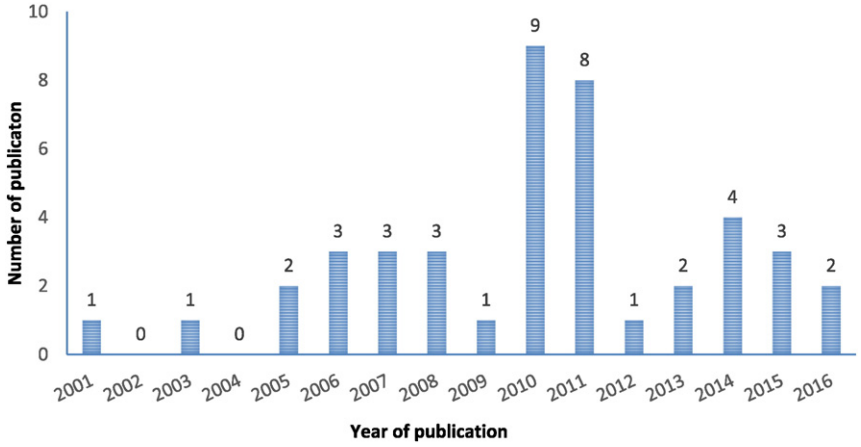


Fig. 1. Number of publications for the determination of PPIs, their metabolites and TPs in waters by means of LC-MS (source: Advanced search in Scopus with title, abstract, keywords: proton pump inhibitor; water; wastewater; environment; liquid chromatography mass spectrometry).

environment, mainly in the water compartment. Residual amounts can reach surface waters, groundwater or sediments. Thus, not only parent PPIs but also their related compounds, such as metabolites and/or TPs, should be investigated in water monitoring programs as this would lead to a more completed estimation of their concentration and occurrence into water bodies as well as their environmental ecotoxicity (Boix et al., 2013, 2014).

Except for human excretion, another main route of PPIs entry into the environment might be the direct disposal from household waste as many people might dispose the remaining and expired pills by pouring them into the toilet (Jiang et al., 2015; Kümmerer, 2009). In addition, the intentional and unintentional disposal of PPIs from the pharmaceutical industry and hospital sewage increases the level of contamination of sewage and surface water.

4. Fate and behavior of PPIs in aquatic environments

Depending on the environmental compartment where PPIs can be found (groundwater, surface water or sediment), as well on the type of plant (WWTPs, drinking water facilities), various transformations can occur, including sorption, transport and biotic or abiotic processes. A vital role in these processes play some important physical and chemical properties of these substances (i.e water solubility, adsorption coefficient ($\log K_{OC}$), bioconcentration ($\log K_{OW}$) and Henry's law constant), which in combination with the specific environmental conditions are normally influence the behavior of PPIs through wastewater treatment as well as its mobility, persistence and bioavailability in the matrix.

Since PPIs, like other pharmaceutical compounds, are designed to resist to microbial degradations and to be chemically stable, (Khetan and Collins, 2007), their abiotic decomposition is the most likely reaction to occur in surface waters. Hence, they are not predicted to be readily biodegraded during wastewater treatment, and hydrolysis and/or photodegradation (Boix et al., 2013; Khetan and Collins, 2007) are expected to be important fate processes in aquatic environments.

Considering the abiotic transformation of PPIs, most of the work has been accomplished as a part of research focusing on the treatment of these compounds and scarce data are available under natural experimental conditions. For example, hydrolysis studies conducted especially on omeprazole and lansoprazole have revealed that their rate of degradation in water solution is dependent on pH. Both compounds were quite stable at neutral or alkaline media (pH 7.0 or 9.0) but their degradation was accelerated in acid conditions decomposing in about 80%

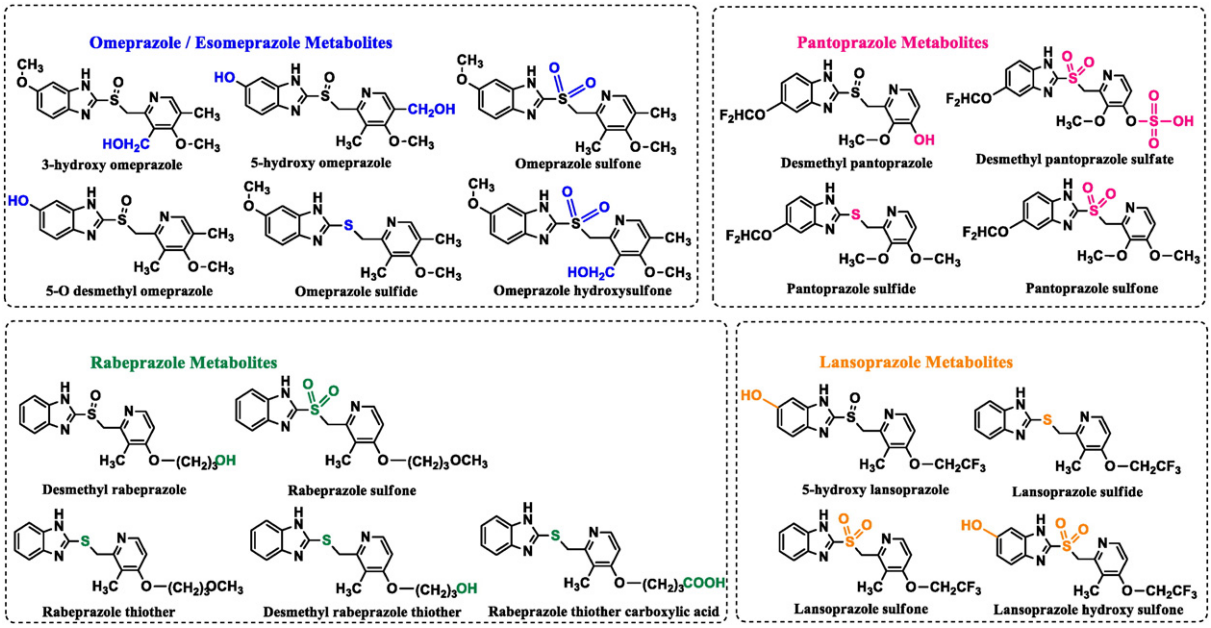


Fig. 2. Main metabolites of PPIs and their structures.

and 40%, respectively (DellaGreca et al., 2006). According to the authors a faster degradation of omeprazole was observed which might be due to the presence of activating groups such as 5-OMe or Me on the pyridinium moiety which should favor the oxidation. The transformation of both compounds gives rise to the generation of sulfide and benzimidazolone derivatices as well as in red-coloured TPs.

When irradiated, the degradation of both drugs is accelerated. After 72 h in milliQ water, lansoprazole was present only for 24% while after 43 h omeprazole was completely degraded. Stability studies of omeprazole revealed also that it is acid labile and sensitive to light and heat (Wallmark and Lindberg, 1987), suggesting rapid transformation at these experimental conditions. By irradiation, the excited drugs undergo a series of transformations forming a number of TPs such as benzimidazoles, dianilines, and pyridines in addition to sulphides, benzimidazolones and the red-coloured TPs. By irradiating the drugs in the presence of additives such as humic acids or nitrate, the same photodegradation yield and TPs were observed indicating insignificant influence on the transformation process (DellaGreca et al., 2006).

A rapid photodegradation was also proposed by our group in a study investigating the photolysis of omeprazole in different natural waters (Kosma et al., 2009). Similarly to the findings of DellaGreca et al. (2006), omeprazole photolysis was highly pH-dependent and degradation was accelerated in acid conditions while it was stable in basic conditions. However, contradictory results have been obtained in investigations of the water matrices tested. Degradation rate of omeprazole was different in natural waters following the order: lake water < sea water < river water < distilled water, implying that it depends on the constitution of irradiated media and probably from the concentration of dissolved organic matter (Kosma et al., 2009). These observed differences may be attributed to the different chemical structures of the tested humic acids (Sigma-Aldrich, naturally occurred humic substances). It is well known that the presence of humic acids can either enhance or inhibit the photodegradation rate depending on their structure, since they can be act either as sensitizers or as inhibitors (scavenger of radicals or light filter consuming most of the photons during the photolysis process), respectively (Sakkas et al., 2001).

In addition to the aforementioned studies, Boix et al. (2013) taking into consideration the fact that omeprazole is among the most consumed pharmaceuticals worldwide, but it scarcely been detected in water, conducted laboratory-controlled experiments to understand the effect of hydrolysis, photodegradation under both sunlight and ultraviolet radiation on the compound and the subsequent generation of its transformation products. As it was expected, a high phototransformation rate of omeprazole was observed, whereas four TPs were detected and could be included as candidates in aquatic environmental monitoring programs instead of the parent compound.

Besides the aforementioned compounds, other PPIs molecules (i.e lansoprazole) are likely to be susceptible to hydrolytic and photolytic reactions in aquatic environment. However, no published data are available and many questions remain to be explored. Therefore, additional research is needed to yield a better understanding of the photolytic transformation of PPIs in the environment. Similarly, biological transformation of PPIs is still unclear since only limited attention has been paid towards their biodegradability in natural environments as well as in biological treatment facilities.

As regards the sorption and the transport of PPIs on solid matrices such as biosolids, manures, soils, and sediments, it is expected to be highly correlated to physico-chemical properties (in particular its lipophilicity, expressed in terms of K_{ow} (octanol water distribution coefficient) and its affinity to the solid phase, expressed in terms of K_d (solid liquid partition coefficient)) and also to geology, soil texture, ambient pH, sediments and DOM (Dissolved Organic Matter) nature. The latter factors have direct impact on their bioavailability, transport by water and transformation rate. Up to date, no data are currently available on the fate and behavior of PPIs to suspended solids or other type of biosolids. However, based on the physico-chemical and fate properties they are not predicted to bound or persistence on biosolids since they are abiotically degraded under environmentally relevant conditions. In addition, based on the calculated logKow, the potential for bioconcentration in aquatic organisms is low (Table 1).

In summary, although, the input of PPIs seems to be of minor importance in the aquatic environment, the impact on the occurrence of their metabolites and/or TPs in the environment is questionable. Thus, the research community urgently needs to focus on understanding the reactivity, fate, transport and persistence of PPIs and their metabolites/TPs in natural systems.

5. Treatment studies of PPIs and their metabolites/TPs

Although, transformations of PPIs under natural conditions have not yet been fully investigated, there are some investigations in chemical engineering studies, which suggest likely routes of PPIs transformation in the natural environment. The following sections will review the relevant literature on such topics and highlight future research directions.

5.1. Removal during wastewater and drinking water treatment

As previously reported, owing to their extensive metabolism in human bodies, PPIs are not expected to be predominantly present in the dissolved aqueous phase of wastewaters. Concerning their removal rates in conventional WWTPs, some scarce data for omeprazole are currently available. For example, a very low removal efficiency of 8.5% has been reported by Rosal et al. (2010) in a WWTP. For the rest of PPI compounds, there is a lack of data on this issue, and thus further research is urgently needed.

5.2. Chlorination

Although the primary purpose of chlorination is the elimination of pathogens, several investigations have shown that chlorine reacts with micropollutants leading to the production of undesired transformation products. Chlorine is a powerful oxidant that oxidizes the organic matter naturally present in water. However, it is not such a strong oxidant to completely mineralize micropollutants and therefore numerous TPs could be generated through oxidation or substitution reactions. Hence, in recent years, several studies have demonstrated the formation of disinfection by-products (DBPs) by the reaction of chlorinated-based disinfectants with different classes of emerging contaminants (ECs) (Armbruster et al., 2015; Jeong et al., 2012; Padhye, 2015).

At present, very limited work has been conducted on this topic and thus there is insufficient information available to reach a final conclusion on the impact of PPIs on the production of DBPs during water chlorination. Specifically, only one study has been published focused on omeprazole, whereas works on other classes of PPIs are scarce. In the study of Boix et al. (2013), the reactivity of omeprazole with chlorine has been investigated during chlorination batch experiments in order to evaluate its ability to give rise to TPs. The obtained results showed high reactivity of omeprazole to chlorine. Through the application of the suspect screening approach, five TPs which would arise from hydroxylation, oxidation and/or chlorination (between one and three chlorine atoms) of omeprazole were detected in positive ionization mode. These compounds were considered by the authors less polar than omeprazole as they eluted later than the parent. Their formation was verified based on their mass accuracy, retention time (t_R) and fragmentation and isotopic pattern. These findings point out that not only the precursor PPI but also the described TPs, should be taken into account in future DWTP monitoring studies. Furthermore, future research in the area of transformation of PPIs with the presence of chlorine in aqueous media should be expanded to a broader range of PPI molecules and aqueous chemistry (e.g. including DOM). Additionally, how the concentrations of bromide in raw waters impact their transformation

and the potential formation of brominated DBPs are critical areas for future research.

5.3. Advanced oxidation processes

Reduction of aquatic environmental levels of PPIs and their metabolites/TPs requires the use of more efficient water treatment technologies. In this respect, advanced oxidation processes (AOPs) are being considered as an alternative to conventional water treatments. AOPs are characterized by the production of hydroxyl radicals (HO•) by diverse reaction systems that oxidize the organic matter present in water. In recent years there is observed a great progress in the field of water treatment by AOPs for a wide range of ECs (Klavarioti et al., 2009). However, research on the photocatalytic treatment of PPIs and the consequential production of TPs is very scarce and only three studies have been published in the literature. In the first study, the photocatalytic degradation of omeprazole was investigated under visible light irradiation by using Y_3NbO_7 nanowires as photocatalyst (Zhao et al., 2015). The obtained results showed that omeprazole photocatalytic reactions followed pseudo-first-order kinetics and Y_3NbO_7 nanowires exhibited greater photocatalytic activity than its bulk counterparts. However, the TPs formed during the photocatalytic process were not investigated. In the second study, the photocatalytic and photoelectrocatalytic degradation of omeprazole on nanocrystalline titania films in alkaline media was systematically investigated (Tantis et al., 2015). Besides the optimization of the parameters affect the photocatalytic efficiency the authors studied also the formed TPs during both processes, by using liquid chromatography high resolution mass spectrometry (LC-HRMS). An omeprazole sulfide TP and the dehydrated derivative of OMP, two well-known hydrolysis TPs of omeprazole, have been identified as major TPs in investigated aqueous matrices and treatments. Furthermore, two more derivatives of omeprazole, assigned as 5-methoxy-1H-benzimidazole and (4-methoxy-3,5-dimethyl-2-pyridyl) methanol were also detected. The first one TP was previously also reported in the electrochemical incineration of omeprazole using platinum or boron-doped diamond anode and in simulated solar photolysis, while the second one is also a well-known hydrolysis and photolysis product of omeprazole. At prolonged irradiation times, omeprazole and its hydrolysis TPs were further degraded into the corresponding pyridine and benzimidazole ring derivates.

Finally, in our study (Kosma et al., 2014a) in which the photocatalytic transformation of omeprazole was investigated by TiO_2 under simulated solar irradiation, a high number of TPs has been elucidated and identified by using a HR-MS LTQ Orbitrap system. Most of them have been previously reported as hydrolysis or photolysis TPs, while some more omeprazole TPs, assigned mainly as di or multi-hydroxyl derivatives have been also identified in the proposed transformation pathways.

6. Analytical methods for the determination of PPIs, their metabolites and their TPs in environmental matrices

Table 2 summarizes the methods applied for the analysis of PPIs and their derivatives in various aqueous matrices. The relevant data was classified according to the target compounds analyzed, the sample preparation and the extraction methods, the LC-MS technique applied for their determination, their limits of detection and finally, their occurrence in the analyzed environmental samples.

6.1. Sample preparation and extraction

In the methods applied for the determination of PPIs (Table 2), the pre-treatment step includes usually various types of glass fiber filters (usually 0.45 μm or 0.7 μm glass fiber filters or nylon membrane filters), depending on the complexity of the sample (Bueno et al., 2010; Gómez et al., 2007; Pedrouzo et al., 2008; Sousa et al., 2011), while in some cases centrifugation is used by applying 4500 rpm for 5–10 min (Boix et al., 2013, 2014, 2015; Gracia-Lor et al., 2010, 2011, 2012).

For the extraction and isolation of PPIs from the aqueous samples, solid phase extraction (SPE) is commonly employed. In most of the cases the choice of SPE sorbent is specific for the compounds of interest. Furthermore, prior to extraction the pH of the samples might be adjusted in a specific value, depending on the chemical properties of the analyzed compounds. Identification of PPIs is usually a part of a larger multiple analysis where various different analytes should also be determined. Therefore, when dealing with multiple target or nontargeted analysis, a compromise is made to gain the best overall recovery (Evans and Kasprzyk-Hordern, 2014). For instance, Gómez et al. (2007) provided a multi residue analytical method for the determination of 20 pharmaceuticals from different therapeutic classes in hospital effluent wastewaters. Among these compounds the occurrence of omeprazole was also studied. In order to optimize the extraction method and due to the different polarity of the compounds, two types of cartridges, in various pH values were tested (Oasis HLB at pH 5, 7 and 8.5 and Oasis MCX at pH 2). For the majority of the compounds, recoveries using Oasis HLB at pH 7 were higher than 75%. Omeprazole showed poor stability at pH below 8 (low recoveries) while it presented high recoveries (77%) when performing an experiment at pH 8.5 and without formic acid in the mobile phase. In addition, extraction of omeprazole with Oasis MCX supposed to be a good choice since it contains amino groups, which are positively charged at pH 2, therefore being bound to the cation exchanger. Nevertheless, in this case only a slight improvement of its recoveries was observed, in contrast with Castiglioni et al. (2005) that reported 50% recovery of omeprazole at the same conditions. Finally, Gómez et al. (2007), refer that in order to extract all analytes in one single step and have a simple and quick method, Oasis HLB in pH 7 conditions were selected. In another study (Van Nuijs et al., 2010), the occurrence of omeprazole and pantoprazole among other pharmaceuticals in influent wastewaters in Belgium took place. The samples were adjusted at pH 2 immediately after collection and stored at −20 °C, while for the extraction of the samples there were also tested various types of sorbents (Oasis HLB at pH 2, 7 and 11, Oasis MCX at pH 2 and Oasis MAX at pH 11). Omeprazole and pantoprazole presented low recoveries when analyzed with Oasis MCX and with Oasis HLB at pH 2 due to their low stability in acid conditions, while Oasis MAX showed high background and interferences for these compounds. Finally, Oasis HLB at pH 7, which is closest to the natural pH of the wastewater was chosen for the sample preparation. Finally, it was reported that omeprazole and pantoprazole were not detected in any of the samples analyzed, due to the fact that the samples were stored at pH 2, where these two compounds were most likely degraded. Van Nuijs et al. (2010) refer also that preliminary experiments with samples that were stored in neutral pH showed the occurrence of omeprazole and pantoprazole in influent wastewater in concentrations up to 50 ng/L.

According to the published literature (see Table 2), from the different SPE cartridges available, the use of Oasis HLB is the most commonly used method for the extraction of PPIs from the aqueous samples. This is due to the fact that HLB cartridge generates the best absolute recoveries for most of the target analytes since it has both hydrophilic and lipophilic properties (Białk-Bielinska et al., 2016; Hao et al., 2007). Samples pH was adjusted usually at neutral pH (Gómez et al., 2007; Gracia-Lor et al., 2010, 2012; Pedrouzo et al., 2008, 2011), or in some cases the extraction was done without pH adjustment since the pH of the analyzed samples was 7–7.5 (Ginebreda et al., 2010; Gros et al., 2006; López-Roldán et al., 2010; Terzić et al., 2008). It is worth noticing that in several studies the pH adjustment was not mentioned at all (Petrovic et al., 2006; Van De Steene et al., 2006). In few cases, other types of SPE sorbents were used. For example, Calamari et al. (2003) used C_{18} cartridges for the determination of omeprazole in river water in Italy, while Van De and Lambert (2008); Van De Steene et al. (2010), and Van De Steene and Lambert (2011) used Speedisk phenyl cartridges for the determination of rabeprazole in surface waters and wastewaters in Belgium.

Table 2
Overview of the LC-MS applications for the determination of the proton pump inhibitors in environmental aqueous matrices.

Parent PPIs, metabolites and TPs	Matrix	Pre-treatment	Sample volume	Extraction method	LC-MS techique	LOD (ng/L)	Concentration	Reference
Omeprazole	River water/influent and effluent wastewater; Germany	Glass fiber filter	1000 mL	SPE (glass cartridge filled with 500 mg of Isolute C18) at pH 7–7.5	HPLC-ESI-MS-MS (QqQ) Column: 100 RP-18 (end capped) (125 mm × 3 mm, 5 μm)	100 ng/L (influent) 25 ng/L (effluent) 10 ng/L (river)	n.d.	Ternes et al. (2001)
	River water; Italy	Glass microfiber filter GF/D 2.7 μm	500 mL	SPE (C18/3 mL, 500 mg) at pH 8	HPLC-MS-MS Column: LUNA C_8 (50 mm × 2 mm, 3 μm)	3.04 ng/L	n.d.	Calamari et al. (2003)
	Effluent wastewater; Italy	Glass microfiber filter GF/D 2.7 μm	500 mL	SPE (Oasis MCX/60 mg) at pH 2	HPLC-ESI-MS/MS (QqQ) equipped with a turbo ion spray source/2 MRM Column: Luna C8 (50 mm × 2 mm, 3 μm)	LOQ: 1.57 ng/L	n.d.	Castiglioni et al. (2005)
	River water and effluent wastewater; Italy	Glass micro-fiber filter GF/D 2.7 μm	500 mL	SPE (Oasis MCX at pH 1.5–2.0)/Lichrolut EN at pH 7.0)	HPLC-MS-MS (QqQ) equipped with a turbo ion spray source/3 MRM Column: Luna C8 (50 mm × 2 mm, 3 μm)		n.d.	Zuccato et al. (2005)
	Effluent wastewater; Spain	Glass fiber filter 0.7 μm	200 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QTRAP (hybrid QqQ/linear ion trap) MS/MS with a turbo ion spray source/3 SRM Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm) and LC-ESI-TOF MS Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm)	2 ng/L (LC-QTRAP MS/MS) 29 ng/L (LC-ESI-TOF MS)	8–922 ng/L	Martínez Bueno et al. (2007)
	Hospital effluent wastewater; Spain	Glass fiber filter 0.7 μm	100 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 7	LC-ESI-TOF-MS Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm-ZORBAX SB-C18)	13 ng/L	2.75–8.69 ng/L	Gómez et al. (2007)
	River water/tap water/influent and effluent wastewater; Spain	Nylon filter 0.45 μm, pH 3	500 mL river 1000 tap water 100 mL influent 250 mL effluent	SPE (Oasis HLB/500 mg) at pH 7	LC-ESI-MS Column: Kromasil 100 C18 (250 mm × 4.6 mm, 5 μm)	5000 ng/L	n.d. (tap and river water) 1110 ng/L and 2170 ng/L (influent) n.d. (effluent)	Pedrouzo et al. (2008)
	River water/influent and effluent wastewater (raw hospital and urban); Spain	Centrifuged at 4000 rpm for 10 min	200 mL river 20 mL influent 40 mL effluent	SPE (Oasis HLB) at pH 2.5	UHPLC-QTOF-MS/MS using an orthogonal Z-spray-electrospray interface Column: Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)		Detected in hospital wastewaters (by post-target analysis)	Ibáñez et al. (2009)
	River water; Spain	Glass fiber filter 0.7 μm	400 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QqQLIT-MS/MS/3 SRM Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm)	0.2 ng/L	n.d. −222 ng/L	Bueno et al. (2010)
	Influent and effluent wastewater (mix of domestic and industrial); Spain	Glass fiber filter 0.7 μm	200 mL influent 400 mL effluent	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QTRAP-MS/MS/2 SRM Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm-ZORBAX SB-C18)	6 ng/L	57–2134 ng/L (influent) <LOQ-922 ng/L (effluent)	Rosal et al. (2010)
	Influent wastewater; Belgium	Glass fiber filter, pH 2	50 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 2	HILIC-MS/MS Column: Phenomenex Luna HILIC (150 mm × 3 mm, 5 μm) equipped with a guard column containing the same	1 ng/L LLOQ (lower limit of quatification)	<LLOQ	van Nuijs et al. (2010)

					stationary phase			
	Influent and effluent urban wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with a *Z*-spray ESI interface/3 SRM Column: Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	11 ng/L (effluent) 29 ng/L (influent)	n.d. (influent) 100 ng/L (max) (effluent)	Gracia-Lor et al. (2010)
	River water and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with an orthogonal *Z*-spray ESI interface/2 SRM Column: Acquity UPLC HSS T3 (100 mm × 2.1 mm, 1.8 μm)	18 ng/L (effluent) 2 ng/L (river)	30 ng/L (max) (effluent) n.d. (river)	Gracia-Lor et al. (2011)
	River water and tap water; Spain	Glass fiber filter 0.7 μm	200 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QTRAP-MS/MS with a turbo ionspray source/3 SRM Column: Reversed-phase C18 (250 mm × 3.0 mm, 5 μm	0.2 ng/L	<1–30 ng/L (river water) n.d. (tap water)	Valcárcel et al. (2011)
	Influent and effluent wastewater; Portugal	0.45 μm mixed cellulose ester filter	50 mL influent 100 mL effluent	SPE (Oasis MX/6 mL, 500 mg) at pH 2	LC–ESI–MS/MS Column: Pursuit UPS C18 (2.1 mm i.d. × 50 mm, 2.4 μm)	n.d.	n.d.	Sousa et al. (2011)
	Influent and effluent domestic wastewater; Spain	Nylon membrane filter 0.45 μm	100 mL influent 250 mL effluent	SPE (Oasis HLB/500 mg) at pH 7	LC-MS-ESI-MS (QqQ)/2 MRM Column: Kromasil 100 C18 (250 mm × 4.6 mm, 5 μm)	10 ng/L (influent) 2 ng/L (effluent)	<LOQ	Pedrouzo et al. (2011)
	Influent and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with a Z-spray ESI interface/3 SRM Column: Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	LOQ (first period of sampling): 10 ng/L (effluent) 30 ng/L (influent) LOQ (second period of sampling): 20 ng/L (effluent) 60 ng/L (influent)	n.d.	Gracia-Lor et al. (2012)
	Sea water; Taiwn	0.7 μm glass fiber filters (GF/F), pH 6, 0.2 g Na_2EDTA	5000 mL	SPE (Oasis HLB/6 mL, 500 mg) at pH 6	HPLC–ESI-MS/MS (QqQ)/2 SRM Column: XDB-C18-ZORBAX Eclipse (150 mm × 4.6 mm, 5 μm)	1 ng/L (deionized water) 2.5 ng/L (sea water)	n.d.	Jiang et al. (2014)
	River water; Taiwan	0.7 μm glass fiber filters (GF/F), pH 6, 0.2 g Na_2EDTA	300 mL	SPE (Oasis HLB/6 mL, 500 mg) at pH 6	HPLC–ESI-MS/MS (QqQ)/2 SRM Column: XDB-C18-ZORBAX Eclipse (150 mm × 4.6 mm, 5 μm)	LOQ: 1.02 ng/L	n.d.	Jiang et al. (2015)
	Surface water and effluent wastewater; Spain	A) Centrifuged at 4500 rpm for 5 min B) Centrifuged at 2500 rpm for 5 min	A) 100 μL direct injection B) 2 mL injection volume to the on line SPE	B) On line SPE (Strata X/2 mm × 20 mm, 25 μm)	A) UHPLC-MS/MS (QqQ) with an orthogonal Z-spray-ESI interface/2 RSM Column: Acquity UPLC BEH (C18100 mm × 2.1 mm, 1.7) B) LC-MS/MS (QqQ) Column: Reversed phase XDB-C18-ZORBAX Eclipse (50 mm × 4.6 mm, 1.8 μm)	1.1 ng/L	n.d.	Boix et al. (2015)
Omeprazole metabolites	Effluent wastewater; Spain		100 mL	SPE (Oasis HLB/60 mg)	UHPLC-(Q)TOF-MS using MS^E approach and an orthogonal Z-spray-ESI interface Column: Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)		Post target identification of 1 omeprazole metabolite (4-hydroxy omeprazole sulfide or 4-desmethoxy omeprazole) in 54% of the samples	Hernández et al. (2011)
Omeprazole/4-OH-omeprazole; 5-O-desmethyl omeprazole	Surface water and drinking		200 mL	SPE (Oasis HLB/6 mL, 200 mg)	UHPLC-MS/MS using Quattro Micro™ QqQ MS with an ESI source Z-spray™/2	Omeprazole: 0.4 ng/L	Surface water: omeprazole: <LOQ-35	Boleda et al. (2013)

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Table 2 (*continued*)

Parent PPIs, metabolites and TPs	Matrix	Pre-treatment	Sample volume	Extraction method	LC-MS techique	LOD (ng/L)	Concentration	Reference
	water; Spain				SRM Column: Acquity BEH C18 (100 mm × 2.1 mm, 1.7 μm)	5-*O*-desmethyl omeprazole: 1.2 ng/L 4-OH-omeprazole: 5.9 ng/L	ng/L 4-OH-omeprazole: <LOQ-60 ng/L 5-*O*-desmethyl omeprazole: not detected Drinking water: n.d.	
Omeprazole/4-hydroxy omeprazole sulfide; 5-hydroxy omeprazole	Surface water and effluent wastewater; Spain		50 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with a Z-spray ESI interface/3 SRM Column: C18 HSS T3 10 cm	Surface water: omeprazole: 2.2–2.8 ng/L 4-hydroxy omeprazole sulfide: 1.9–2.7 ng/L 5-hydroxy omeprazole: 2.2–3.3 ng/L Effluent wastewater: omeprazole: not estimated due to the standard degradation 4-hydroxy omeprazole sulfide: 19.6–60.1 ng/L 5-hydroxy omeprazole: 9.5–60.1 ng/L	Surface water: omeprazole: n.d. 4-hydroxy omeprazole sulfide: <LOQ-0.028 ng/L 5-hydroxy omeprazole: 0.004 ng/L Effluent wastewater: omeprazole: not estimated due to the standard degradation 4-hydroxy omeprazole sulfide: 0.06–0.29 ng/L 5-hydroxy omeprazole: 0.12–0.25 ng/L	Gracia-Lor et al. (2014)
omeprazole TPs	River water and effluent wastewater; Spain	Glass fiber filter 0.7 μm, pH 3	Injection of 10 μL	The extracts were filtered with a 0.45 μm PTFE syringe filter to remove suspended solids and particulate matter and were subsequently analyzed by LC-ESI-QTOF-MS (direct injection analysis)	LC-ESI-QTOF-MS Column: Reversed phase C8-Zorbax Eclipse XDBC8 (50 mm × 4.6 mm, 1.8 μm)		Non target identification of 4 omeprazole metabolites in river samples	López et al. (2014)
Omeprazole/17 omeprazole TPs	Surface water/urban influent and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL/50 mL	SPE (Oasis HLB/60 mg) at pH 7 SPE (Oasis MCX/60 mg) at pH 2	UHPLC-QTOF MS using an orthogonal Z-spray-ESI interface Column: Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm) and UHPLC-MS/MS QqQ with an orthogonal Z-spray-ESI interface/2 RSM Column: Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)		Omeprazole: nd. 2 TPs were detected by QTOF and 4 TPs were detected by QqQ	Boix et al. (2013)
Omeprazole/24 omeprazole metabolites	Surface water/urban influent and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL/50 mL	SPE (Oasis HLB/60 mg) at pH 7 SPE (Oasis MCX/60 mg) at pH 2	UHPLC-QTOF MS using an orthogonal Z-spray-ESI interface Column: Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm) UHPLC-MS/MS (QqQ) with an orthogonal Z-spray-ESI interface/2 RSM Column: Acquity UPLC BEH C18 (100 mm		Omeprazole: n.d. 9 metabolites were detected by QTOF and 14 metabolites were detected by QqQ	Boix et al. (2014)

					× 2.1 mm, 1.7 μm)			
Omeprazole/23 omeprazole metabolites	Influent wasteater; Italy	Glass microfiber filter GF/A 1.6 μm and a mixed cellulose membrane filter 0.45 μm	25 mL	SPE (Oasis MCX/3 mL, 60 mg) at pH 2	HPLC-LTQ-Orbitrap-MS using a micro-spray mode Column: Zorbax SB-C18 (150 mm × 0.5 mm, 5 μm)		Omeprazole: n.d. 6 omeprazole metabolites were detected	Boix et al. (2016)
Omeprazole/17 omeprazole TPs/33 omeprazole metabolites (with available reference standards of 4-OH omeprazole sulfide and 5-OH omeprazole)	Effluent wastewater; Athens	Glass fiber filter 0.7 μm	200 mL	SPE (StrataX/200 mg)/a mixture of Strata WAX (100 mg), Strata WCX (100 mg) and IsoluteENV + (150 mg) at pH 6.5 ± 0.2	UHPLC-QTOF MS using an orthogonal Z-spray-ESI interface Column: Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)		Omeprazole: n.d. 3 omeprazole metabolites were detected (among them 4-OH omeprazole sulfide)	Ibáñez et al. (2016)
Esomeprazole	Treated wastewater; India	Whatman filter paper (No 41)	250 mL	SPE (PSDVB)	HPLC-UV–Vis Column: BDS Hypersil C8 (4.6 mm × 250 mm, 5 μm)	90,000 ng/L	n.d.	Kumar and Samnani (2010)
Lansoprazole	Surface water and wastewater; Spain	Wastewaters: glass-fiber filters 1 μm/nylon-membrane filters 0.45 μm; Surface waters: 0.7 μm and 0.45 μm filters	500 mLsurface 100 mL influent 200 mL effluent	SPE (Oasis HLB/60 mg, 3 mL and 200 mg, 6 mL) without pH adjustment	LC–MS–MS (QqQ) with a Z-spray ESI interface/2 MRM Column: Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, 5 μm) and a C18 guard column	5 ng/L (surface water) 8 ng/L (effluent 14 ng/L (influent)	<LOD (surface water, influent and effluent)	Gros et al. (2006)
	River water/influent and effluent wastewater; Spain, Croatia	Glass-fiber filters 1 μm/nylon-membrane filters 0.45 μm	500 mLsurface 100 mL influent 200 mL effluent	SPE (Oasis HLB/3 mL, 60 mg)	UHPLC-Q-TOF-MS Column: Acquity C18 (50 mm × 2.1 mm, 1.7 μm)	120 ng/L	n.d.	Petrovic et al. (2006)
	Urban and industrial wastewater/river water; Spain	Wastewaters: glass-fiber filters 1 μm/nylon-membrane filters 0.45 μm; River: 0.7 μm and 0.45 μm filters	500 mLsurface 100 mL influent 200 mL effluent	SPE (Oasis HLB/3 mL, 60 mg) at natural sample pH	LC–QqQ–MS/MS in SRM mode Column: Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, 5 μm) and a C18 guard column	5 ng/L (river water) 8 ng/L (effluent) 14 ng/L (influent)	n.d.	Gros et al. (2007)
	Municipal and industrial wastewater; Croatia, Bosnia and Herzegovina, Serbia	Glass-fiber filters 1 μm/nylon-membrane filters 0.45 μm	100 mL influent 200 mL effluent	SPE (Oasis HLB/3 mL, 60 mg) without pH adjustment	LC–ESI–MS/MS operating in SRM mode Column: Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, 5 μm) and a C18 guard column	14 ng/L	<LOD	Terzić et al. (2008)
	River water; Spain	Nylon membrane filters 0.45 μm	500 mL	SPE (Oasis HLB) without pH adjustment	LC–QqQ–MS/MS in SRM mod Column: Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, 5 μm) and a C18 guard column	0.6 ng/L (SRM 1) 2.5 ng/L (SRM 2)	42–76.7 ng/L	López-Roldán et al. (2010)
	River water and one of its tributaries; Spain	Nylon membrane filters 0.45 μm	400 mL	SPE (Oasis HLB) without pH adjustment	LC–ESI–MS/MS operating in SRM mode Column: Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, 5 μm) and a C18 guard column	5 ng/L	<LOD	Ginebreda et al. (2010)
	River water; Spain	Glass fiber filter 0.7 μm	400 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QqQLIT-MS/MS with a turbo ionspray source/3 SRM Column: Reversed phase C18 (250 mm × 3.0 mm, 5 μm)	2 ng/L	n.d-96 ng/L	Martínez Bueno et al. (2010)
	River water and tap water; Spain	Glass fiber filter 0.7 μm	200 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 8	LC-QTRAP-MS/MS with a turbo ionspray source/3 SRM	2 ng/L	<8–961 ng/L (river water)	Valcárcel et al. (2011)

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Table 2 (*continued*)

Parent PPIs, metabolites and TPs	Matrix	Pre-treatment	Sample volume	Extraction method	LC-MS techique	LOD (ng/L)	Concentration	Reference
					Column: Reversed phase C18 (250 mm × 3.0 mm, 5 μm)		n.d. (tap water)	
	Surface water and drinking water; Spain		200 mL	SPE (Oasis HLB/6 mL, 200 mg)	UHPLC-MS/MS using Quattro Micro™ QqQ MS with an ESI source Z-spray™/2 SRM Column: Acquity BEH C18 (100 mm × 2.1 mm, 1.7 μm)	1.6 ng/L (surface water) 1.2 ng/L (drinking water)	48–53 ng/L (surface water)	Boleda et al. (2013)
Lansoprazole enantiomers (+)-LAN and (−)-LAN	Wastewater samples collected from the discharge along a river; Brazil	Nylon membrane filters 0.45 μm, methanol LC (3 drops) added	Direct injecion of 1000 μL		2DLC-IT–MS/MS eqquiped with ESI source/3 MRM Columns: A bovine serum albumin octyl column (RAM-BSA C8) was used in the first dimension for the exclusion of the humic substances, while a polysaccharide-based chiral column was used in the second dimension for the enantioseparation	150 ng/L	n.d.	Barreiro et al. (2011)
Pantoprazole	Influent wastewater; Belgium	Glass fiber filter, pH 2	50 mL	SPE (Oasis HLB/6 mL, 200 mg) at pH 2	HILIC-MS/MS Column: Phenomenex Luna HILIC (150 mm × 3 mm, 5 μm) equipped with a guard column containing the same stationary phase	1 ng/L LLOQ (lower limit of quatification)	<LLOQ	van Nuijs et al. (2010)
	Influent and effluent urban wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with a Z-spray ESI interface/3 SRM Column: Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	33 ng/L (effluent) 66 ng/L (influent)	n.d. (influent) 180 ng/L (max) (effluent)	Gracia-Lor et al. (2010)
	River and sea water/effluent wastewater; Germany	Samples settled at 4 °C in the dark for 12–24 h and the supernatant was used for analysis	500 mL river 500 mL sea 100 mL effluent	SPE (Oasis HLB/6 mL, 500 mg) at pH 7 ± 0.2	HPLC–ESI–MS/MS (QqQ) in MRM mode Column: Polaris C18-Ether (150 mm × 2 mm, 3 μm)	4.8 ng/L (surface water) 36 ng/L (effluent)	13 ± 2.8 ng/L (river water) n.d. (sea water) 149 ± 23 ng/L (effluent)	Nödler et al. (2010)
	River water and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with an orthogonal Z-spray ESI interface/2 SRM Column: Acquity UPLC HSS T3 (100 mm × 2.1 mm, 1.8 μm)	4 ng/L (effluent) 2 ng/L (river)	36 ng/L (max) (effluent) 117 ng/L (max) (river)	Gracia-Lor et al. (2011)
	Influent and effluent wastewater; Spain	Centrifuged at 4500 rpm for 5 min	100 mL	SPE (Oasis HLB/60 mg) at neutral pH	UHPLC-MS/MS (TQD) with a Z-spray ESI interface/3 SRM Column: Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	LOQ (first period of sampling): 30 ng/L (effluent) 70 ng/L (influent) LOQ (second period of sampling): 4 ng/L (effluent) 60 ng/L (influent)	First period: n.d. (influent) 50–180 ng/L (effluent) Second period: n.d. (influent) 10–20 ng/L (effluent)	Gracia-Lor et al. (2012)
	Surface water and drinking water; Spain	Nitrocellulose membrane filter 0.45 μm	Direct injection of 20 μL	No preconcentration nor purification process were required	LC–ESI–MS/MS with a Xevo TQS tandem quadruple MS equipped with an orthogonal Z-spray ESI source/2 MRM Column: Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	2 ng/L	20 ng/L and 50 ng/L (river water) n.d. (drinking water)	Luque-Espinar et al. (2015)
	Surface water and effluent wastewater; Spain	A) Centrifuged at 4500 rpm for 5 min B) Centrifuged at 2500 rpm for 5 min	A) Direct injection of 100 μL B) 2 mL	B) On line SPE (Strata X/2 × 20 mm, 25 μm)	A) UHPLC-MS/MS (QqQ) with an orthogonal Z-spray-ESI interface/2 RSM Column: Acquity UPLC BEH (C18100 mm × 2.1 mm, 1.7)	0.1 ng/L	n.d. −7 ng/L (effluent) n.d. −1 ng/L (surface water)	Boix et al. (2015)

			injection volume to the on line SPE		B) LC-MS/MS (QqQ) Column: Reversed phase XDB-C18–ZORBAX Eclipse (50 mm × 4.6 mm, 1.8 μm)			
Pantoprazole enantiomers (+)-PAN and (−)-PAN	Wastewater samples collected from the discharge along a river; Brazil	Nylon membrane filters 0.45 μm, methanol LC (3 drops) added	Direct injecion of 1000 μL		2DLC-IT–MS/MS eqquiped with ESI source/3 MRM Columns: A bovine serum albumin octyl column (RAM-BSA C8) was used in the first dimension for the exclusion of the humic substances, while a polysaccharide-based chiral column was used in the second dimension for the enantioseparation	200 ng/L	150 ng/L/180 ng/L (effluent) 13 ng/L (river)	Barreiro et al. (2011)
Rabeprazole	Surface water; Begium	Glass fiber filter 1.5 μm/membrane filter 0.4 μm in a SolVac holder	100 mL	SPE (Oasis HLB/6 mL, 200 mg)	LC–ESI–MS/MS/2 SRM Column: Chromolith Performance RP-18 (4.6 mm × 100 mm) with a C18 guard column (2 mm × 4 mm)			Van De Steene et al. (2006)
	Surface water/influent and effluent wastewater; Begium	Glass fiber filter 1.5 μm/membrane filter 0.4 μm in a SolVac holder	100 mL surface 10 mL influent 10 mL effluent	SPE (Speedisk phenyl cartridges/100 mg, 3 mL) at pH 7	LC–ESI–MS/MS/2 SRM Column: pentafluorophenyl (PFP) (100 mm × 4.6 mm, 5 μm) with a Metaguard precolumn (Pursuit PFP 4.6 mm, 5 μm)	0.5 ng/L	<LOD	Van De Steene and Lambert (2008)
	Surface water/influent and effluent wastewater; Begium	Metrigard glass fiber filter 0.5 μm in a SolVac holder	100 mL	SPE (Speedisk phenyl cartridges/100 mg, 3 mL) at pH 7	LC–ESI–MS/MS/2 SRM Column: pentafluorophenyl (PFP) (100 mm × 4.6 mm, 5 μm) with a Metaguard precolumn (Pursuit PFP 4.6 mm, 5 μm)	0.5 ng/L	<LOD	Van De Steene et al. (2010)
	Surface water (brook); Belgium	Metrigard glass fiber filter 0.5 μm in a SolVac holder	100 mL	SPE (phenyl cartridges/100 mg, 3 mL) at pH 7	UHPLC–ESI–MS/MS/2 SRM Column: VanGuard Pre-Column Acquity UPLC HSS T3 (5 mm ×2.1-mm, 1.8 μm) and an Acquity HSS T3 column (100 mm × 2.1 mm, 1.8 μm)	0.5 ng/L	<LOD	Van De Steene and Lambert (2011)

n.d: not detected.

Finally, the large-volume injection (LVI), an attractive approach has been also applied for determination of PPIs in wastewaters as a rapid and efficient alternative to conventional SPE. Typically, LVI involves the direct injection of sample volumes that range from 100 to 5000 μL versus the more conventionally injected volumes of 10–20 mL. Despite, the important advantages (e.g. higher sensitivity, high sample throughput at minimal cost, good reproducibility and low sample contamination) offered by the minimal sample handling, some drawbacks (e.g. deterioration of peak shape for early eluting analyte, high matrix effect in complicate matrices) put into question its use in non-clean samples. Therefore, the use of modern and sensitive instruments is commonly needed. An interesting example of the latter approach is that presented by Boix et al. (2015) for the simultaneous quantification and confirmation of 40 human and veterinary pharmaceuticals and drugs of abuse in effluent wastewater and surface samples, including omeprazole and pantoprazole. The direct injection of water samples (100 μL) on UHPLC–MS/MS QqQ system, without any previous sample treatment, has been shown as an attractive approach as it avoids time consuming sample preparation steps and reduces the amounts of solvents used (Farré et al., 2012). Satisfactory accuracy and precision were obtained in recovery experiments at three concentration levels in two kinds of water matrices, EWW and SW, using 10 different samples to this aim. Recoveries were ranged between 93% and 118% for both compounds, while the LOQs were <1.1 ng/L.

Besides LVI, direct injection without preconcentration or purification process has been also performed for determination of omeprazole and pantoprazole or their TPs, based on the high sensitivity of the analytical technique used (LC-MS/MS). In the study of López et al. (2014), direct injection of the samples in the chromatograph, after the appropriate filtration, took place in order to determine omeprazole TPs in river water and effluent wastewaters in Spain. Direct injection is cited also by Barreiro et al. (2011) for the determination of lansoprazole and pantoprazole isomers in wastewaters in Brazil and by Luque-Espinar et al. (2015) for the determination of pantoprazole in surface water and drinking water in Spain. These last reports illustrate quite well the advantages of direct injection in terms of easy sample handling. Considering the high sensitivity and selectivity of the recent LC-MS/MS approaches, the authors concluded that the direct injection in some cases could be an effective way for the determination of the target known or unknown compounds. Future trends are towards direct injection in order to reduce time consume and human labor.

6.2. Identification by liquid chromatography-mass spectrometry

6.2.1. LC separation

In terms of LC separation, it is important to ensure the highest quality data. Reversed-phase LC (RP-LC) has been commonly used for the separation of PPIs before mass spectrometric detection using ESI source as interface (Hao et al., 2007; Masiá et al., 2014). Standard C_8 or C_{18}, >3 μm, >3 mm i.d., >150 mm long LC columns were widely used for the identification of PPIs in many cases (Jiang et al., 2014; Kumar and Samnani, 2010; Martínez Bueno et al., 2007; Rosal et al., 2010; Valcárcel et al., 2011). In the last years, miniaturization of the LC columns has taken place in order to increase sensitivity and peak resolution efficiency as well as shorten time analysis of the samples. Hence, reduction of the inner diameter of the LC columns or the particle size has been done (Masiá et al., 2014). Under this aspect, PPIs confirmation was done in many cases with columns applying smaller diameters (normal bore columns from 4.6 to 2.1 mm) which offer better ESI compatibility and lower mobile phase consumption. Nevertheless, the introduction of ultra high performance liquid chromatography (UHPLC) columns (diameters below 2 μm) is the most important development in recent years (Hernández et al., 2014). These columns shorten the run time and facilitate chromatographic resolution in order to minimize co-elution of compounds with close *m/z* values. Furthermore, narrower and higher peaks can be obtained which facilitates the detection of the target analytes (Hernández et al., 2014; Vazquez-Roig et al., 2013). For the identification of the PPIs and specifically for the identification of their metabolites/TPs in most of the studies UHPLC columns are used (Boix et al., 2013, 2014, 2015; Gracia-Lor et al., 2010, 2011, 2012; Hernández et al., 2011; Ibáñez et al., 2009).

Besides HPLC and UHPLC, the utility of chiral LC coupled with tandem MS in the context of improved screening assays for enantiomeric compounds which normally have insufficient separation in typical reversed phase LC systems has been recently demonstrated. A nice example in this field is the recent study of Barreiro et al. (2011), where a rapid and sensitive method for the simultaneous quantification of pantoprazole and lansoprazole enantiomers fractions in native aqueous samples been recently developed and validated by using a two-dimensional LC system coupled to ion-trap tandem mass spectrometer (2DLC-IT–MS/MS). A restricted access media of bovine serum albumin octyl column (RAM-BSA C_8) was used in the first dimension for the exclusion of the humic substances, while a polysaccharide-based chiral column was used in the second dimension for the enantioseparation of both pharmaceuticals. The overall procedure, employing a small amount (1.0 mL) of native water sample per injection, provided good selectivity, extraction efficiency, accuracy, and precision with detection limits of 0.200 and 0.150 μg L^{-1} for the enatiomers of pantoprazole and lansoprazole respectively.

6.2.2. MS detection and identification

Since LC-MS allows the simultaneous determination of heterogeneous mixtures of contaminants with different physicochemical characteristics, the majority of the methods developed until now for the determination of PPIs in environmental samples are based on LC coupled to tandem MS using triple quadrupole (QqQ) analyzers. Due to the fact that monitoring only one transition might result in false positive, identification of each compound requires at least two transitions (Krauss et al., 2010). Hence, analysis was performed using SRM (selected reaction monitoring), employing at least two of the highest characteristic transitions. The precursor ion ($[M + H]^+$/($[M - H]^-$), the two SRM transitions, together with the retention time and the ion intensity ratios, give sufficient information for the determination of the unknown compounds (Białk-Bielinska et al., 2016; Hernández et al., 2014). According to literature at least two product ions were monitored for each of the PPIs, while in some cases more than two products were used. For instance, Gracia-Lor et al. (2010) monitored three product ions for the determination of omeprazole (*m/z* 198.1; 136.1 and 158.1) and pantoprazole (*m/z* 200.1; 138.1 and 153.1) in wastewaters in Spain by using triple quadrupole TQD for the analysis, while Gracia-Lor et al. (2014) reported also three product ions for the identification of omeprazole metabolites 4-hydroxy omeprazole sulfide (*m/z* 168.2; 149.2 and 136.2) and 5-hydroxy omeprazole (*m/z* 152.1; 214.0 and 196.2), in surface waters and effluent wastewaters in Spain, by means of TQD with an orthogonal Z-spray-electrospray interface. It is worth noticing that generally, all PPIs are found to be positively charged ($[M + H]^+$), except for lansoprazole which has also been reported to be negatively charged ($[M - H]^-$) by the group of Petrovic et al. (2006).

ESI interface, operating in positive ionization (PI) mode worked well and is the ionization mode of choice. The matrix-induced signal suppression and isobaric spectral interferences from the sample that affect the sensitivity of the method are among the major drawbacks of this mode that should be always taken into consideration (Farré et al., 2012; Krauss et al., 2010). In order to provide a more accurate measurement and to overcome some of these difficulties, isotopically labeled analogues as surrogate standards have been proposed in most of the reported methodologies for complex sample analysis.

Besides QqQ, linear traps and new generation Time of-flight MS (TOF-MS) instruments have been also employed (Masiá et al., 2014; Vazquez-Roig et al., 2013). Meanwhile, the use of HR-MS (Q-TOF and hybrid linear ion trap (LTQ) FT Orbitrap mass spectrometer) is steadily increased in recent years and have been also successfully performed

either for structure elucidation or/and screening and quantification of PPIs and their TPs in aqueous environmental samples (Boix et al., 2013, 2014, 2016; Boleda et al., 2013; Gómez et al., 2007; Gracia-Lor et al., 2014; Hernández et al., 2011; Ibáñez et al., 2009, 2016; Kosma et al., 2014a, 2014b; López et al., 2014; Martínez Bueno et al., 2007; Petrovic et al., 2006; Ibáñez et al., 2016). More specifically, in a very interesting study, LC coupled to HR LTQ Orbitrap MS was performed for the identification of omeprazole and 23 metabolites of omeprazole in Italian municipal influent wastewater (Boix et al., 2016). According to the authors, at first, the samples were processed using data depended acquisition method (DDA), where the first data event was a full-scan MS and the next six data events were MS^2 of the six most intense ions, based on the target list of metabolites which have already been identified (urine or wastewater), in previous study by mean of UHPLC-QTOF MS (Boix et al., 2014). Due to the fact that DDA did not provide reliable information in all cases (maybe due to the complexity of the matrix), a further experiment was done in order to obtain fragmentation for the compounds that tentatively identified in the first analysis. Finally, the results showed that omeprazole was not present at any sample but six of its metabolites were identified. From the metabolites identified the metabolite corresponding to 4-OH omeprazole sulfide was the only one for which an analytical standard was available, so its identity could be further confirmed (present in 60% of the samples). In addition, the isomer of omeprazole with *m/z* 346.1225 ($C_{17}H_{20}N_3O_3S^+$) was found in 16 of the 30 samples, hence its presence highlights the availability of good chromatographic separation in order to avoid confusion with the parent omeprazole since they have two same fragment ions (198.0584 and 149.0710) (Boix et al., 2016). In a previous study, Boix et al. (2014) studied first the detection and elucidation of omeprazole metabolites in urine by means of LC-QTOF MS. After the elucidation of 24 metabolites, continuously their occurrence in surface water, influent and effluent wastewaters in Spain took place. The samples have been analyzed by LC-QTOF MS and LC-MS/MS QqQ. The results showed that parent omeprazole was not detected at any sample. After LC-QTOF MS analysis of water samples, nine metabolites were detected in water samples, while these results were confirmed by LC-MS/MS QqQ analysis, which allowed the detection of 14 metabolites. Boix et al. (2014) reported also the presence of omeprazole isomer, which presented the same exact mass (*m/z* 346.1225) and a same major common fragment (*m/z* 198.0589) with parent omeprazole, as the most frequent compound (detected in 80% IWW, 90% EWW and 41% SW with LC-QTOF MS and in 100% IWW, 100% EWW and 48% SW with LC-MS/MS QqQ).

In other recent works (Hernández et al., 2011; López et al., 2014) a non-target analysis for the identification of omeprazole metabolites in waters by means of LC-QTOF-MS was reported. Hernández et al. (2011), reported the occurrence of 1 omeprazole metabolite (4-hydroxy omeprazole sulfide or 4-desmethoxy omeprazole) in 54% of the effluent wastewaters in Spain, while López et al. (2014), reported the occurrence of four metabolites in river samples in Spain.

Except for the application of HRMS for the detection of omeprazole metabolites in waters, the use of UHPLC-MS/MS QqQ has also been reported. Boleda et al. (2013) studied the occurrence of omeprazole and its metabolites 4-OH-omeprazole and 5-O-desmethyl omeprazole in surface and drinking water in Spain, using commercial available standards. In addition Gracia-Lor et al. (2014) reported the identification of omeprazole and its metabolites 4-hydroxy omeprazole sulfide and 5-hydroxy omeprazole in surface waters and effluent wastewaters in Spain, using also commercial available standards. Confirmation of the analytes identity was guaranteed by acquiring three SRM transitions and evaluating their Q/q ratios and retention time. Concentrations of omeprazole and its metabolites found in waters will be discussed in Section 7.

In continuation of their previous research attempt concerning the degradation/transformation of omeprazole in water samples under hydrolysis, photodegradation and chlorination, Boix et al. (2013) conducted the "*suspect screening*" approach to search omeprazole and its identified 17 TPs in real surface water and urban wastewater samples by using both LC-QTOF-MS and LC-(ESI)-MS/MS QqQ systems. The findings revealed the absence of omeprazole in all the 52 tested water samples despite its wide consumption. On the other hand, two TPs were detected with QTOF on the basis of the accurate mass of the protonated molecules. In addition, their occurrence was confirmed by means of LC-MS/MS QqQ which also made feasible the detection of another two TPs. Omeprazole sulfide with the accurate mass *m/z* 330.1271 was found to be the most frequently detected among the suspect TPs, being present in 90% of the effluents and in 26% of the surface waters. The presence of this TP has also been reported in wastewaters in Greece (Kosma et al., 2014b). Boix et al. (2013) suggest that this TP should be included in future works instead of the parent omeprazole in order to have a more realistic review of omeprazole's impact in the environment. Finally, a very interesting collaborative work, between the University of Athens and University Jaume I of Castellon, was recently published (Ibáñez et al., 2016) performing a broad investigation on the presence of TPs/metabolites of pharmaceuticals in effluent wastewaters from Athens using LC-QTOF MS. Specific TPs of pharmaceuticals previously identified in degradation experiments at laboratory scale including omeprazole metabolites were monitored. Additionally, a homemade database was widened to around 450 compounds (corresponding to 100 parents), including theoretical exact masses of metabolites/TPs reported in the literature. The UHPLC-QTOF MS analysis of treated Greek urban wastewater has confirmed the detection and identification of 34 TPs/metabolites of pharmaceuticals, including three omeprazole metabolites (omeprazole OM7d ($C_8H_7N_3O_3$), omeprazole OM10 ($C_8H_7N_3O_3$) or 4-hydroxy omeprazole sulfide).

Overall, the simultaneous determination of a broad number of compounds in one injection, with a corresponding reduction of time and costs, without the need for reference standards make the "*suspect screening*" approach one of the current trends in environmental analytical chemistry. Its significance and its nearly ideal combination with HRMS systems, has rapidly been recognized and a further rapid increase in monitoring studies are anticipated in the near future.

Besides the well-established advantages of the "*suspect screening*" approach, other approaches such as isotopic pattern recognition (IPR), background subtraction (BS), mass defect filtering (MDF) and constant neutral loss filtering (CNLF) and characteristic fragment ion recognition (CFIR) have been also used as assistant tool for metabolite/TP characterization and identification of many pharmaceutical compounds (Lambropoulou and Nollet, 2014). Owing to difference of various metabolites/TPs in their chemical structure, approaches are usually different in metabolite/TP screening and identification. Therefore, it is more important to determine whether single approach or multiple approaches to be used for specific metabolite/TP, so that many metabolites/TPs could possibly be accurately identified as possible. Based on this, a neutral loss acquisition approach has been explored for the studied PPIs by using HR-MS orbitrap system. The full mass range of fragments generated from all precursors was scanned after a standard injection of omeprazole, lansoprazole, pantoprazole and rabeprazole. A list of observed neutral loss values is depicted in Fig. 3. By using the Fragment ion searching this approach was performed for detection of possible metabolites/TPs of omeprazole in real wastewater samples (Fig. 4). Overall, using the combination of high resolution accurate mass and ion fragmentation, the utility of neutral loss analysis becomes very powerful and can be successfully used as a systematic strategy to global identification of multiple components and metabolites and TPs in environmental samples.

7. Occurrence of PPIs and their metabolites/TPs in the aquatic environment

The application of the methods analyzed in the previous sections revealed the occurrence of the five PPIs, and some of their metabolites/TPs, in different environmental aqueous matrices (Table 2). These

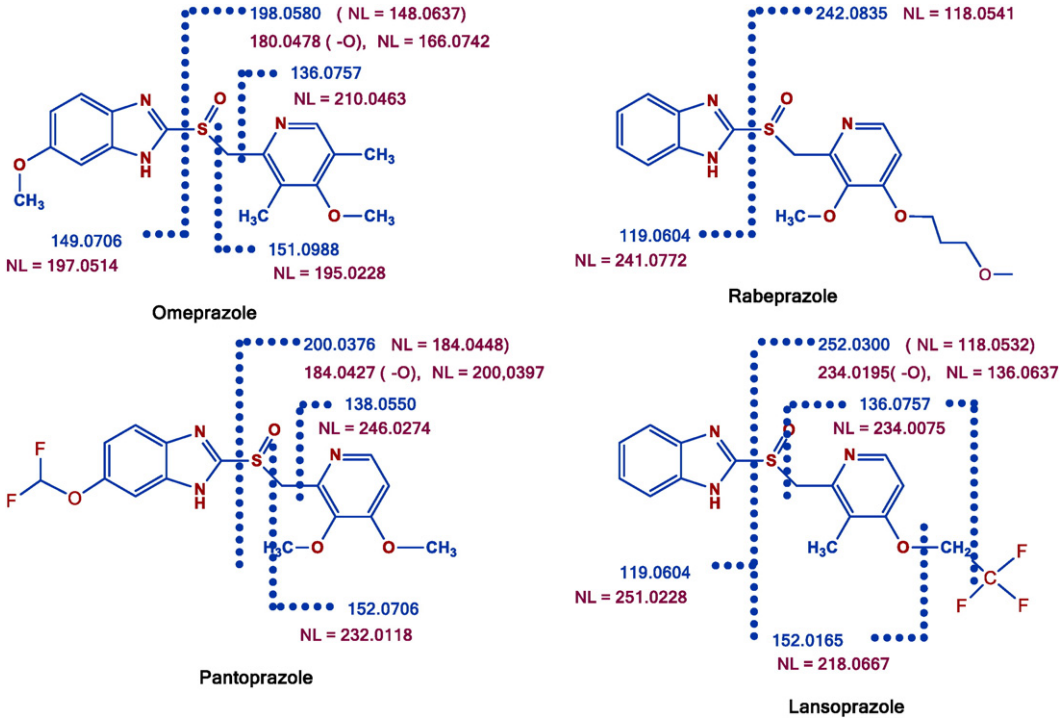

Fig. 3. Fragments and associated neutral loss values used for PPIs.

compounds were found in a wide range of water samples, including surface water, sea water, wastewater and drinking water, in concentrations up to several ng L^{-1}. Omeprazole was the most frequently studied PPI compound. Additionally, the occurrence of its metabolites and TPs in various aqueous matrices was also studied. In most of the studies omeprazole was not detected at the samples analyzed may be due to the fact that it is found to be acid labile and sensitive to light and heat (Boix et al., 2013, 2014, 2015, 2016; Castiglioni et al., 2005; DellaGreca et al., 2006; Gracia-Lor et al., 2012; Jiang et al., 2014, 2015; Sousa et al., 2011; Ternes et al., 2001; Zuccato et al., 2005). Nevertheless its occurrence is reported in some studies, with concentrations ranging in surface waters from below quantification limit (<LOQ) (Boleda et al., 2013) to 222 ng/L (Bueno et al., 2010), in influent wastewaters from <LOQ (Pedrouzo et al., 2011; Van Nuijs et al., 2010) to 2170 ng/L (Pedrouzo et al., 2008), in effluent wastewaters from <LOQ (Pedrouzo et al., 2011; Van Nuijs et al., 2010) to 922 ng/L (Rosal et al., 2010), while it was not detected in sea water (Jiang et al., 2014) or in drinking (or tap) water (Boleda et al., 2013; Pedrouzo et al., 2008; Valcárcel et al., 2011). In some cases, the concentration variability of omeprazole from site-to-site could also be attributed to regional prescribing customs and usage fands, population density, contexts of water treatment technology capabilities as well as seasonal and environmental climatic conditions. For instance, Bueno et al. (2010), which found the highest concentrations of omeprazole in surface waters, reports that the samples were collected from the most developed and densely populated area of Spain (Madrid), about 8050 km^2 with a population of about 6 million, were the streams run through several residential, industrial and agricultural areas. Furthermore, in a WWTP of Madrid, which treats a mixture of

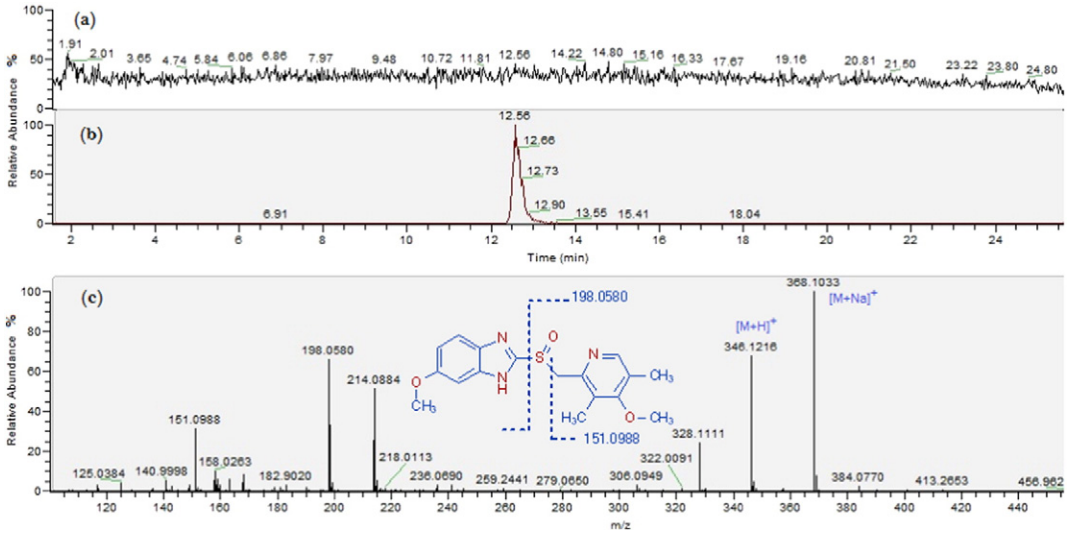

Fig. 4. Detection of omeprazole in hospital WWI sample (Ioannina city) by using and LTQ Orbitrap system. (a) Total ion chromatogram, (b) Extracted ion chromatogram at *m/z* 346.1211, (c) MS spectra.

domestic and industrial wastewaters from facilities located near the city with a nominal capacity of 3000 m^3/h of a raw wastewater, omeprazole was found at high concentrations in the influents (2134 ng/L), as well as in the effluents (922 ng/L) (Rosal et al., 2010).

In few studies, commercial available omeprazole metabolites allowed the quantification of them in the aqueous samples. For instance, Gracia-Lor et al. (2014) reported concentrations ranging from LOQ-0.028 ng/L and 0.004 ng/L, for 4-hydroxy omeprazole sulfide and for 5-hydroxy omeprazole respectively, in surface waters, while reported also 0.06–0.29 ng/L and 0.12–0.25 ng/L, for 4-hydroxy omeprazole sulfide and for 5-hydroxy omeprazole, respectively, in effluent wastewaters, in Spain. Furthermore, Boleda et al. (2013) found concentrations ranging from <LOQ-60 ng/L for 4-OH-omeprazole, in surface waters in Spain, while 5-O-desmethyl omeprazole was not detected. In the same study, both 4-OH-omeprazole and 5-O-desmethyl omeprazole were not present in drinking waters. Other studies refer only the qualitative analysis of omeprazole's metabolites and TPs (Boix et al., 2013, 2014, 2015; Hernández et al., 2014; López et al., 2014) (Fig. 5).

The identification of esomeprazole was reported only in one study in effluent wastewaters in India (not detected) by Kumar and Samnani (2010). Lansoprazole, which was also found to be unstable in water (DellaGreca et al., 2006), was detected in surface waters in concentrations between below limit of detection (<LOD) (Gros et al., 2006; Terzić et al., 2008) and 961 ng/L (Valcárcel et al., 2011), while it was not detected in drinking water. In addition, it was found in concentrations <LOD in wastewater samples (Barreiro et al., 2011; Gros et al., 2006, 2007; Petrovic et al., 2006; Terzić et al., 2008).

As for the other two PPIs concern, pantoprazole was determined in influent (<LLOQ) and effluent wastewaters (10–200 ng/L) (Gracia-Lor et al., 2012), as well as in surface waters (13–117 ng/L) (Gracia-Lor et al., 2011; Nödler et al., 2010). Finally, the occurrence of rabeprazole is reported to be studied by Lambert's group, in surface waters and wastewaters in Belgium, which was detected only in concentrations <LOD, maybe due to the fact that is found to be unstable under acid conditions (Van De Steene et al., 2006, 2010; Van De Steene and Lambert, 2008, 2011).

8. Predicted concentrations of PPIs in aquatic environment and environmental risks

In order to investigate the possible environmental risks of the class of PPIs, investigations could be attained by using models to predict concentrations of pharmaceuticals in aquatic environment the so-called predicted environmental concentrations (PEC). Based on this aspect, a retrospective environmental risk assessment study of PPIs was conducted by Woldegiorgis et al. (2009) in the Nordic countries during the period 1997–2007, concerning surface water. In particular, initially a retrospective environmental risk assessment was made based on the sales over the preceding decade (based on PEC/PNEC-quotients) in surface water. Furthermore, in an attempt to also account for differences in biodegradation rate between different top-selling drugs, a 'time resolved' PEC/PNEC equation has been introduced. The approaches used by the authors to evaluate the risks are described in detail in Supplementary material. The authors concluded that PPIs do not impose any environmental risk (risk quotients $\ll 1$). In addition, although an increase in the environmental risk by a factor of 10 is observed for Sweden during the period, the calculating risk for a substance at the time would not reveal that fast increase in the risk. Furthermore, it is worth noticing that when assessing the environmental risks, the ecotoxicity tests and the corresponding values (NOEC, EC_{50} or even LC_{50}) reflect acute toxicity testing and that PPIs may in fact also trigger receptors in aquatic organisms that regulate the proton flux in lumen.

In addition, Valcárcel et al. (2011) studied the risk assessment of omeprazole and lansoprazole in specific points of the main rivers of the Madrid Region and they found that omeprazole presented low acute potential hazard in fish based on its hazard quotients (HQs) ($0.1 < HQ < 1$), while lansoprazole presented no adverse effect in algae ($HQ < 0.1$). On the other hand, Ortiz de García et al. (2014) studied

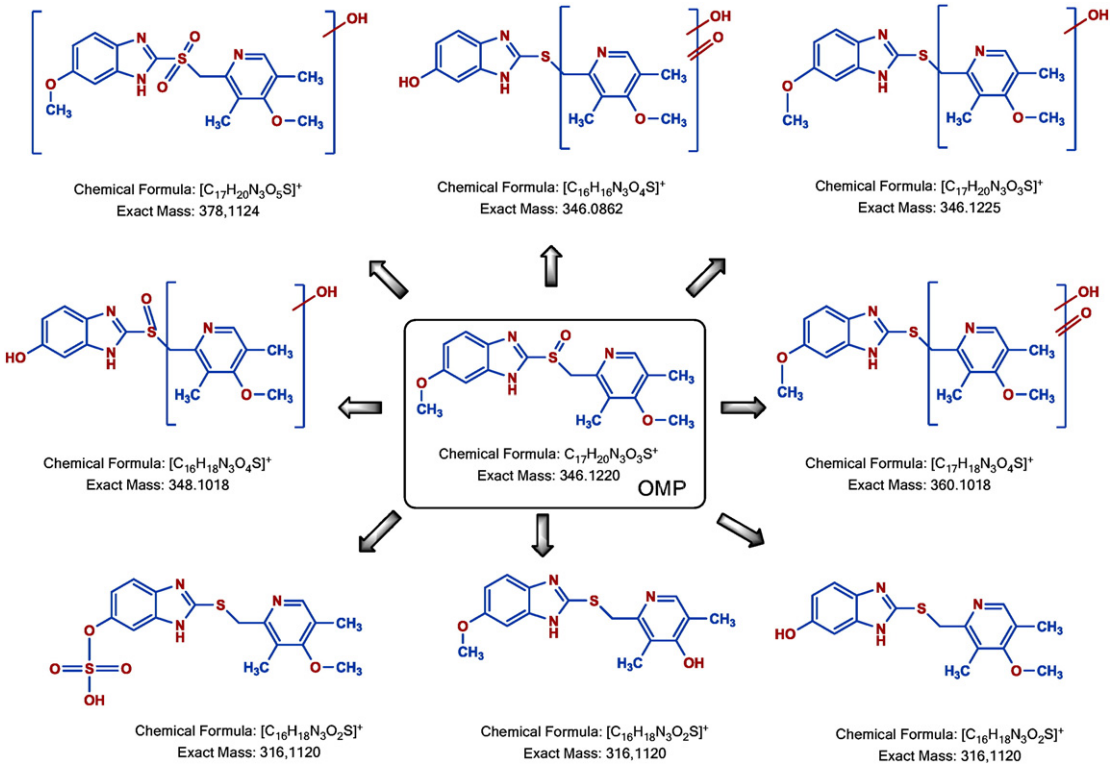

Fig. 5. Major metabolites of omeprazole identified in wastewaters (Boix et al., 2014).

Table 3
Risk quotients (RQs) for omeprazole and lansoprazole estimated for fish, invertebrates and algae in surface water and effluent wastewater taking into consideration the worst case scenario (highest concentration). Lowest available toxicological data for fish, invertebrates and algae are presented as well as the assessment factor (AF) applied in each case.

Compound	Fish	Invertebrates	Algae	Data	AF	RQ effluent wastewater			RQ surface water		
						fish	Invertebrates	Algae	fish	Invertebrates	Algae
Acute toxicity											
Omeprazole	12[a]	1.068[a]	1.009[a]	EC50 (mg/L)	1000	0.0768	0.863	0.937	0.0185	0.207	0.220
Lansoprazole	18[b]	22[b]		LC50 (mg/L)	1000				0.0533	0.0436	
Chronic toxicity											
Omeprazole	23.2[c]	50[c]	<1.81[c]	NOEC (mg/L)	10	0.00039	0.00018	0.0050	0.0000956	0.0000444	0.00122

Note: RQ of omeprazole estimated from concentrations 0.922 μg/L in effluent wastewater (Martínez Bueno et al., 2007), and 0.222 μg/L in surface water (Bueno et al., 2010), while RQ of lansoprazole estimated from concentration 0.961 μg/L in surface water (Valcárcel et al., 2011), in Spain.
[a] Valcárcel et al. (2011).
[b] Sanderson and Thomsen (2009).
[c] Holm (2007).

the ecotoxicity of 26 pharmaceuticals in Spain (among them omeprazole), based on the ecotoxicity values obtained by bioluminescence and respirometry assays and by predictions using the US EPA ecological structure–activity relationship (ECOSAR™). Using (European Medicines Agency) EMEA guidelines, the real risk of impact of omeprazole in WWTPs and in the aquatic environment was predicted. According to the results, omeprazole showed some type of risk for aquatic environments (RQ > 1 in some cases) and for activated sludge from the secondary treatment of WWTPs (harmful to aquatic organisms, according to Globally Harmonized System of Classification and Labelling of Chemicals - GHS).

The aforementioned results were further compared by environmental risk data based on measured concentration levels in real surface and wastewater samples cited in the present review. For this purpose, a first approach of the risk assessment for the aquatic environment was performed according to the European guidelines (European Commission, 2003) by comparing the measured environmental concentration (MEC) to the toxicologically relevant predicted no-effect concentrations (PNEC). Taking into account a worst-case scenario, maximum concentration levels of omeprazole and lansoprazole detected in surface wasters and wastewater effluent have been evaluated (Table 3). The calculated data showed RQ ratio values <1, reflecting a low to medium risk for omeprazole and low potential risk for lansoprazole. The highest risk of omeprazole has been obtained for algae and invertebrates in effluent wastewaters, with RQ values of 0.937 and 0.863, respectively, implying that omeprazole, for these two species, may poses an acute hazard risk when occurring in high amounts measured in the environment. Meanwhile, comparing findings arising from both predicted model studies and measured concentrations, it is apparent, that the potential environmental risk of PPIs may be higher in some cases than that suggested by predicted model studies of the parent compounds.

In summary, at present, there is insufficient information available to reach a final conclusion on the impact of omeprazole and lansoprazole in the environment. In addition, due to the scarcity of ecotoxicological data, a full environmental risk assessment cannot be properly executed for all PPIs. Moreover, there is a lack of data on the effects issues associated with additives effects and interactions (synergism/antagonism) including both parent compounds and metabolites/TPs. Therefore, more ecotoxicological research is needed in order to more accurately assess the risks of these drugs in the environment.

9. Conclusion, future trends and perspectives

Despite the high input of PPIs in the environment, only a handful of studies have been conducted over the last years dealing with their environmental fate focused mainly on omeprazole and less to lansoprazole. However, all of them revealed the rapid transformation of these compounds under light and acid conditions.

From the analytical point of view, a number of sensitive and efficient analytical methods for determination of PPIs (in particular for omeprazole and pantoprazole) in environmental aqueous matrices has been developed in recent years, based primarily on SPE approach coupled to low (LC-MS/MS QqQ) or HR-MS systems (LC-MS QToF, LTQ Orbitrap). Taking this into account it is safe to conclude that the absence of PPIs in the water samples seems not to be related to analytical issues but to human metabolism and/or degradation/transformation of these compounds in the aquatic environment. This statement is further supported by recent systematically monitoring studies in which occurrence of omeprazole at trace levels is revealed.

Omeprazole attended the most frequent analysis and some knowledge and predictions regarding its behavior and its metabolites/TPs in the environment have been gathered in recent years; however, for other PPI compounds and their metabolites/TPs, information on occurrence, distribution, fate and effects in the environment is to a big extent still unknown. Hence, further occurrence, exposure and toxicological input is required to provide a more comprehensive picture of the impact of PPIs in the environment as well as to perform reliable environmental risk assessment not only for the parent compounds but also for their metabolites/TPs. With respect to ecotoxicity data gaps, there has been demonstrated a need for the evaluation of omeprazole metabolites and TPs on non-target organisms, since these types of contaminants have been gradually detected in the environment due to improvements of analytical techniques. Finally, guidelines for ERA of pharmaceuticals need to incorporate specific chronic tests and new endpoints that reflect the mode-of-action of the compounds.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.06.160.

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