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Review

Storage of natural water samples and preservation techniques for pharmaceutical quantification

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ABSTRACT

In order to perform a human and ecological risk assessment of pharmaceutical products (PPs) in natural waters, it is necessary to accurately quantify a broad variety of PPs at low concentrations. Although numerous currently implemented analytical methodologies, less is known about the preservation of PPs in natural water samples within the period before analysis (holding time, storage conditions). This paper is the first literature review about the stability of PPs in natural waters (surface and groundwaters) during sample storage. The current work focuses on a comparison of the performances of the available preservation techniques (filtration, container materials, storage temperature, preservative agents, etc.) for PPs in samples. All 58 reviewed PPs may be successfully stabilized during 7 days in surface waters by at least one appropriate methodology regarding temperature, acidic and non-acidic preservatives. When temperature is not a sufficient preservation parameter for some PPs (hormones and fluoxetine) its combination with the addition of chemical agents into the samples may prolong the integrity of the PPs during storage in surface water. There is a strong need to use standard protocols to assess and compare the stability of PPs in environmental water matrices during storage as well as during analytical preparation or analysis (European criteria 2002/657/EC). Since the stability of PPs during sample storage is a critical parameter that could call into question the quality of the data provided for the concentrations, the design of stability studies should rigorously take into account all critical parameters that could impact the concentrations of the PPs with time.

Contents

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1. Introduction

In recent decades, the presence of Pharmaceutical Products (PPs) (human or veterinary) in natural waters has increasingly raised worldwide concerns (public, scientists, and regulators) about their possible risks for aquatic fauna and flora as well as for human beings. There are a myriad of PP contamination sources in the aquatic environment as described in the literature [1–3]. However, the major contamination pathways for human and veterinary PPs to enter into water bodies are respectively from household wastewater effluents and their soil transfer after soil amendment by biosolids and liquid waste from treated animals. A PP is a bioactive compound that may occur in the water cycle not only in its initial form (i.e. ingested and then excreted in parent form), but also as its metabolites, and/or transformation products produced in the environment and during wastewater and raw drinking water treatment processes (via abiotic and biodegradations). A broad variety of PPs (parent and transformation products) have been widely detected, albeit at low concentrations (i.e. ng/L), in surface waters, groundwaters and stream waters all over the world [4–12]. Within the EU Water Framework Directive, it has recently been proposed to add three pharmaceutical substances, i.e. 17α-ethinyloestradiol, 17β-oestradiol (E2), and diclofenac, to the list of 33 pollutants regulated in EU waters [13]. In order to examine the potential risk of PP contamination for animals and humans, it is necessary, among other tasks, to assess and monitor the release of PPs to the aquatic environment.

There is a considerable commitment to this issue thanks to the broad analytical development and implementation of new advanced methodologies that allow the identification and quantification of PPs in natural waters up to low ng/L range. In addition, efforts are currently being undertaken to implement new standard methodologies at the national scale to monitor the concentrations of PPs in natural waters [14,15]. Surprisingly, only a few studies have dealt with the stability and preservation of samples containing PPs although numerous works have published information on the performance of developed analytical methodologies and many occurrence data are reported in the literature [16–20]. Because one prerequisite of research is the accurate estimation of real concentrations of PPs in water matrices, questions arise as to how long and how to store and preserve PPs in natural water samples so that they are not depleted before analysis. Ideally, sampling and sample analysis should be carried out within one day to avoid the stability issue of PPs. Nevertheless, there are often logistical hindrances that oblige environmental laboratories to store water samples for a longer period of time before their analysis.

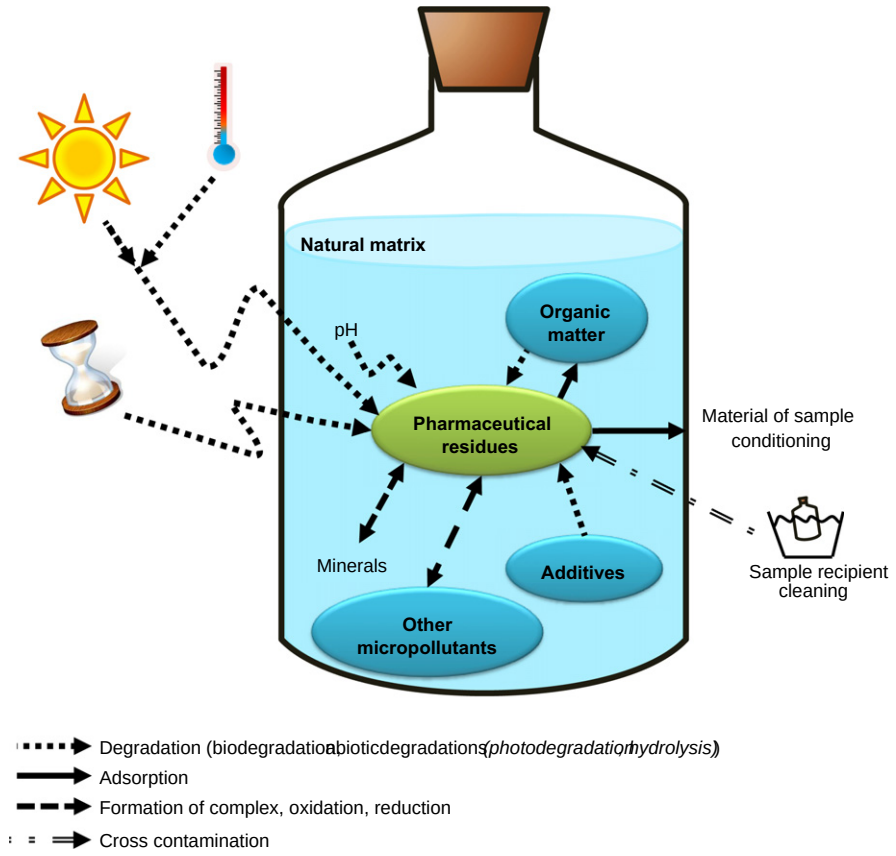

Fig. 1. Sources and processes (possibly) affecting the stability of PPs in samples before analysis.

However, new sampling methodologies, such as passive sampling or in situ extraction (e.g. solid phase micoextraction – SPME, stir bar sorptive extraction – SBSE), allow PPs to be freed from water matrices thus, avoiding, to some extent, problems of PP stability in natural waters before analysis step. Yet, the preservation of PPs in sorbents (SPME, SBSE) or during passive sampling [21–24] may generate other PP stability issues that are not represented within the scope of this review.

This review focuses on a comparison between reviewed studies on natural water samples, which was somewhat difficult given that different protocols (regarding protecting samples from light, sample bottle materials, filtrations, analytical instruments and procedures (e.g. LC–MS/MS, GC–MS/MS), corrections for the concentrations with/without isotope labelled standards, etc.), statistical analyses (i.e. various combinations of statistical tests) and interpretation approaches for the results (sometimes the data are not shown) were used.

The differences in the PP concentrations for the water samples recovered at the initial time before storage and the concentrations at the end of the test period may result from a significant effect of the storage conditions and/or analytical uncertainties. A significant (mean) loss of $\pm 20\%$ in the concentrations of the PPs was arbitrarily chosen for the purpose of this review as the absolute critical limit in order to point out the instability of the PPs during a given storage time as it has been decided in a previous stability study adapted from the American standard guide ASTM D4841 [25]. It is important to note that all published studies that reported a percentage loss within the range of $\pm 20\%$ were considered as negligible in this review because of possible misinterpretation which might be attributable to the potential measurement uncertainties of the analytical methodologies.

Therefore, the main goal of this work is to review the available preservation techniques for PPs in grab water samples from their transportation after field sampling up to the analysis stage. It focuses on the description of sources parameters and processes that may notably influence the preservation of PPs in natural waters during samples storage. Furthermore, it compares and discusses the performances of existing preservation techniques which represent a challenge in terms of developing mutiresidual analytical methodologies so as to produce the most robust and accurate data possible, thereby reflecting the real concentrations of the PPs in the aqueous matrices.

Based on the reported stability results, this review suggests recommandations to preserve the integrity of the PPs in the samples until analysis, highlighting the need for further research on this issue.

2. Target PPs and processes affecting the stability of pharmaceutical products in natural water samples from sampling up to analyses

Eigthy-one molecules belonging to 15 therapeutic classes (human and veterinary uses) have been focused on in several recent studies (from 2000 to the present) reporting stability results on the storage and preservation of PPs in surface water and groundwater water samples. Seventy percent of these PPs are mainly represented, in terms of the number of molecules, by steroid hormones (36%: oestrogens, progestogens and androgens), antibiotics (24%: macrolides, pyrimidins, β-lactamins, quinolones, sulfonamides, etc.) and antidepressants and anxiolytic drugs (10%). The remaining 30% of the investigated PPs cover 12 therapeutic classes such as non-steroidal antiinflammatory drugs (NSAIDs), anticonvulsants, lipid regulators, β-blockers, anticancer drugs, etc. Only 25% molecules (20 PPs) from the 81 targeted PPs are dedicated to veterinary uses, 12 of which are both human and veterinary PPs and only seven of which are exclusively veterinary drugs (florfenicol, melengestrol, melengestrol acetate, nandrolone, oxolinic acid, sulfadimethoxine, zearalanol) according to the list of authorized veterinary drugs in France [26]. These observations, regarding the issue of PPs in the environment, correlate with the need for current research to prioritize the most relevant PP markers among the several thousand human and veterinary PPs released on the market.

On the basis of the specific therapeutic activities for which PPs are designed, PPs have different structures as well physical and chemical proprieties (acido-basic dissociation, solubility in water, polarity, etc.) that may be involved in many depletion processes in natural water sample containers after sample collecting. Although PPs are described as persistent pollutants in aqueous environments, some previous studies have demonstrated attenuation phenomena that may occur in aqueous environments [2,27–29]. To some limited extent, these published studies legitimize the fact that we cannot rule out the possible decrease of PP concentrations in a sample bottle of natural water during storage. Before developing a protocol for a stability test, it is thus important to identify the sources and to understand the processes that may be critical for stability of PPs during storage before analysis. Fig. 1 represents the main sources and processes that may impact the stability of PPs in a natural water sample. Because PPs mostly contain highly or mid-polar molecules, the evaporation of the PPs is the least expected phenomenon to occur in water samples.

2.1. Adsorption

PPs may be subjected to adsorption onto organic matter (OM) (suspended matter, colloids) in natural water samples as well as in the environment [30,31] but also to adsorption onto the sampling container surface which may bias the PP concentrations results. This issue is especially decisive in the assessment of PP concentrations in an aqueous environment at the low nanogram per litre level. In both cases, the adsorption strength of the PPs depends not only on the proprieties of the bottle material or the suspended matter and the hydrophobicity of the PPs, but it also depends on the characteristics (structure, pK_a, solubility, etc) and concentrations of the PPs, the matrix composition (salinity, pH, etc.), the temperature, the volume to contact area ratio and the contact time. PPs with higher hydrophobic proprieties ($\log K_{ow} > 4$, e.g. steroidal hormones) are the main candidates for adsorption onto OM or the sample container surface. The major part of PPs is hydrophilic compounds that have a rather low *n*-octanol/water distribution coefficient ($\log K_{ow} < 4$) [1]. However, the other factors cited above may also govern the adsorption of PPs, such as the speciation of the PPs which depends on the pH of natural waters and may create attractive or repulsive interactions with the OM [1,32–34] or with the weak acidic silicate and silanol groups on the surface of untreated glass bottles [35]. Moreover, desorption from OM of PPs naturally sorbed to the OM would result in an overestimation of the real concentrations in the dissolved phase of the water samples. Particular attention must therefore be paid during sample storage to avoid the sorption of PPs onto the material container and to prevent the promotion of sorption/desorption onto the OM; furthermore, additional studies should be undertaken to understand the mechanisms that play a role in the sorption of PPs onto natural water sample material.

2.2. Degradation (photo- and bio-degradation, hydrolysis)

Depending on the composition and temperature of the water matrix according to the composition (bacteria, fungus, spore,

virus, algae, etc.) and the amount of microorganisms, PPs are susceptible to biodegradatation under stereoselective catabolic processes; however, information on the bio-transformation pathways and by-products is still needed as it could be very helpful in the preservation of natural samples [1,36,37]. A recent study has proved that microbial activity in water samples was the main reason for the degradation of some hormone PPs during the storage of surface water samples, confirming observations in previous studies [38–40]. Since the elimination of PPs by microoganisms seems to represent a relevant strategy technique that should be investigated in order for water managers to reduce environmental contamination by PPs as reported in some studies [41], biodegradation thereby constitutes an obstacle to be overcome when trying to determine reliable concentration of PPs in natural waters.

The solar irradiation of PPs in natural water samples during transportation and storage may also undergo abiotic transformations inducing the depletion of PPs in samples prior to analysis. Photodegradation depends not only on the light exposure but also on the exposure duration and frequency and the matrix with particular attention on the nature and content of the OM [1,2]. PPs may be transformed directly by the absorption of ambient light. Indirect photodegradation may also be induced in the presence of light exciting the OM (humic and fulvic acids, nitrate, etc.) which, as a photosensitizer, may create radicals that might react in turn with the PPs [1,42–44].

Hydrolysis is another degradation pathway that might reduce the concentration of the PPs during sample storage. It depends on the ability of the structure of the PPs determining their stability in water and their reactivity to be cleaved into by-products in the natural water matrices. For instance, Jiang et al. suggested that the constitutive β-lactam amide bond of cepholosporins is particularly unstable regarding hydrolysis, which depends on the pH of the water matrix [45].

2.3. Other chemical abiotic transformations

According to their ionic speciation, which is intrinsically linked with the pH of the matrix, numerous PPs (e.g. quinolones, NSAIDs) are expected to form some complexes with cationic metals (Cd^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}, Fe^{2+}, Ca^{2+}, Mg^{2+}, Al^{3+}, etc.) in water [46–48]. In addition, it can be assumed that the formation of a complex would favour the adsorption of the PPs onto the glassware if this kind of container material is used for sample storage. Other possible interactions (electrostatic, hydrogen bounding, etc.) between PPs as well as between PPs and other micropollutants or all additive agents necessary to carry out the analytical procedure would require particular attention to preserve the stability of PP in samples. For instance, surfactant agents from detergents contaminating environmental waters may modify the adsorption/desorption equilibrium onto OM in natural water samples [32]. A loss of PPs may also be attributed to oxidation/reduction reactions; thus, experimental investigations need to be conducted to fully understand this in order to manage the preservation of PPs in natural water samples. Given that few studies have reported the racemization or inter-conversion of chiral PPs or PP deconjugation in natural waters, it is presumed that the results for the PP concentrations in the samples are erroneous in these cases, although these processes are still largely unknown for many PPs in natural water matrices [36,39,49,50].

2.4. Cross-contamination

If sample containers are not cautiously or properly cleaned before sampling, this might be a source of false positive results or could results in the overestimations of PP concentrations due to a possible cross-contamination of PPs during one sampling campaign after another. The analysis of additional blank samples filled by pure water when field sampling would ensure the absence of contamination during sampling and transport to the laboratory whereas these blank samples do not provide enough information to determine the eventual sources of contamination as suggested in Capdeville et al. [51]. In any case, samples also must be preserved in air and water-tight bottles once sampled to prevent all potential cross-contamination.

3. Shipping, storage conditions and holding time

3.1. Shipping conditions

It is advisable to comply with basic precautions during transport following sampling in order to safeguard PPs in water samples up until they arrive in the laboratory. With respect to the ISO 5667-3 guidelines on the handling of water samples, samples have to be protected and kept in air and water-tight recipients to prevent sample alteration, leakage and external contamination [1]. Immediately after collection, samples are usually transported within the shortest delay possible in iceboxes while avoiding all sources of light exposure to minimize PP degradation and, adsorption as much as possible until the samples arrive in the laboratory for further pre-treatments, storage and analysis.

3.2. Storage conditions and holding time

3.2.1. Impact of light

Numerous and various PPs are photolabile in natural waters, for examples: diazepam, sulfonamides, fluoxetine, diclofenac, triclosan, albuterol, fenofibrate, iodoarene, fluoroquinolones, tetracyclines, tylosin, nitrofuran antibiotics, 17β-oestradiol, etc. [52–56]. However some PPs such as oxolonic acid may not be sensitive to sunlight in surface water samples [57].

Instructive information on the photostability of PPs is given in medical and pharmacological literature although it cannot be accurately extrapolated to the more complex matrices of environmental water [58]. The impact of light exposure on some PPs in samples has been studied within the framework of assessing the process conditions for analyzing PPs in natural waters whereas this was not done in natural water [39,49]. The results of six replicates of deionized samples in unsilanized clear and amber glass spiked with 19 PPs were compared in Vanderford et al. [39]. The data for all 19 analytes showed a negligible percentage loss (below 20%) after 14 days of storage in amber as well in clear glass bottles at 4 °C. Conversely, the percentage loss of eight oestrogens and two progestogens in samples exposed to ambient light and temperature irradiations ranged from 20% to 100% (with a median loss increasing up to approximately 34%) after one week (for gestodene) [49]. Although the contribution of temperature to the degradation of PPs was not evaluated in this study, the control samples were stored at 4 °C and the tested light exposed samples were stored at ambient temperature. The last two cited studies emphasize the importance of implementing an assessment of the influence of light on the stability of PPs in natural samples in parallel to the analytical development. Because environmental research studies are often focused on a multi-residual approach, a non-transparent material should therefore be used as a recipient during all steps (including storage) from sampling to analysis whereas it is generally preferred for most of the organic pollutants. These basic precautions could be a way to sustain the concentration of the PPs during storage since there has been no

Table 1
Tests conditions to study the effect of temperature on PPs in aqueous samples.

Analytes	Number of replicates (*n*)	Bottle material	Spiking concentration (ng/L)	Pre-treatment before storage	Storage conditions	Test duration	Tested temperatures	Remark(s)	Ref.
Ketoprofen, Salicylic acid, Diclofenac, Gemfibrozil	n.m.	Amber glass	1000	None	n.m.	8 days	+4 °C, RT	–	[67]
Oxolinic Acid, Trimethoprim Florfenicol, Sulfadiazine	6	Polyethylene	10 and 100	None	n.m.	56 days	−20 °C, +5–7 °C	Data not shown	[86]
Ibuprofen, Naproxen, Ketoprofen, Diclofenac	3	Polyethylene	Between 83 and 1124	Filtration on 2.7 μm and 0.45 μm glass fibre filter	n.m.	7 days, 10 days	+4 °C, RT	• Samples homogeneized in polyethylene bucket after being sampled in pyrex borosilicate glass containers • Results not shown	[87]
Erythromycin, Trimethoprim, Ciprofloxacin, Ofloxacin, Sulfamethoxazole	3	Amber glass	Between 100 and 200	None	Dark	2, 7, 10 days	+4 °C, RT	Each replicate analysed in duplicate	[88]
Ciprofloxacin, Oxolonic acid	3	Low-density polyethylene	1000	None	Dark	124 days	−18 °C, +4 °C, RT	–	[57]
Trimethoprim, Sulfamethoxazole, Ibuprofen, Naproxen, Diclofenac, Carbamazépine, Phenytoin, Primidone, Fluoxetine, Diazepam, Meprobamate, Gemfibrozil, Iopromide, 17β-Oestradiol, Progesterone, Testosterone, Oestrone, 17α-Ethynyloestradiol, Atenolol	6	Amber glass	n.m.	None		72h, 28–35 days	−20 °C, +4 °C, RT	–	[39]
Azithromycin Clarithromycin, Erythromycin–H2O, Roxithromycin, Trimethoprim, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfamethizole, Sulfamethoxazole, Sulfapyridine, Sulfathiazole	n.m.	Amber glass	n.m.	Filtration (glass fibre filter, 90 mm diameter (GF/F, Whatman)	Dark	7 days	RT	• Sampling with stainless steel bucket. Samples then transferred onto amber glass bottle • Data not shown	[68]
17β-Oestradiol, Oestrone, Oestriol, Zearalanol, Zearalenone, Zearalanone, Testosterone, 5α-androstan-17β-ol-3-one, Androsterone, 5α-androstane-3,17-dione, 4-androstene-3,17-dione, Boldenone, Nandrolone, 17β-trenbolone, 17α-trenbolone, Progesterone, 17,20-dihydroxyprogesterone, Melengestrol, Melengestrol acetate	3	Silanized Amber glass	1 000	None	Dark	14 days	+4 °C	• Samples of SW refer to "aged run-off" that was stored 4 months before PPs spiking for stability study	[64]

n.m.: not mentioned, SW: surface water, DiW: deionized water, RT: room temperature.

conclusion about the influence of light on PPs in natural water samples.

3.2.2. *Impact of containers materials*

The sample container type may bias the results of the PP concentrations in natural water as a result of PP adsorption onto the sample container surface. Bottles are commonly used to sample natural waters and their constituent materials have to be clean and inert to prevent the loss of PPs in natural waters and to prevent modifications to the sample composition. A range of various bottle materials used in natural water sampling have been described in the literature: silanized and unsilanized (amber) glass bottles, high and low density polyethylene bottles (HDPE and LDPE, respectively), polypropylene bottles, and unspecified glass bottles [38,59,60]. Only a few studies have described the impact of bottle material on PPs [39,49,61]. Furthermore, to the extent of the authors' knowledge, no study has addressed the impact of bottle material on PPs with regards to the surface water matrix.

The three studies that have already compared the recoveries of PPs in deionized water filled bottle made of different materials as a function of time (i.e. 7, 14 and/or 28 days) have all demonstrated that sample containers type may affect PPs recovery [39,49,61]. Moreover, they determined that there is not one single container material that can universally recover all PPs without a significant change over time. The best choice of bottle material clearly depends on the target analytes.

The U.S. Environmental Protection Agency revised the conditions to preserve PPs in water samples in its EPA Methods 1694 and 1698 [14,62] based on a later study in which different bottle materials were tested on approximately 87 PPs belonging to 19

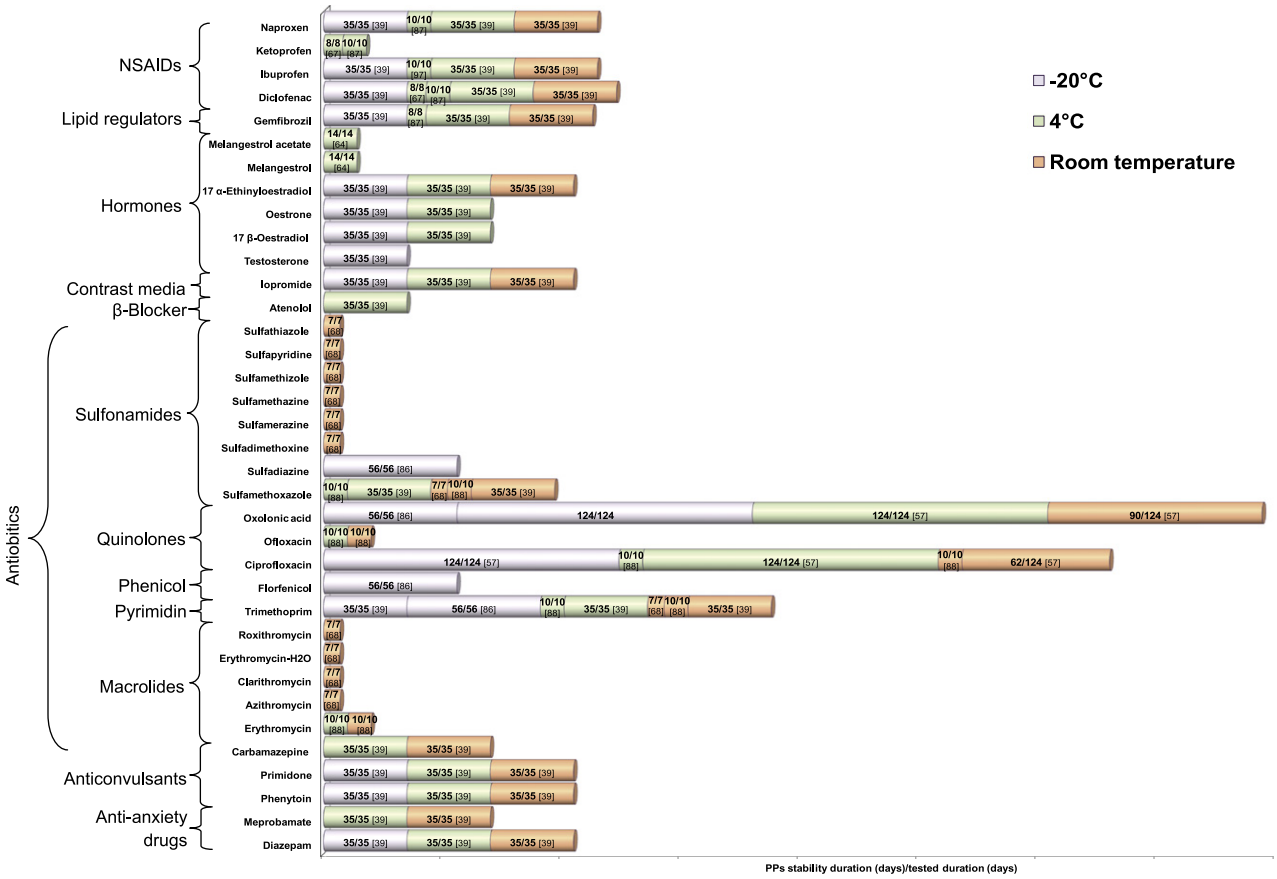

Fig. 2. Stability duration of PPs in surface water samples as a function of storage temperature.

therapeutic groups in deionized water. Despite the differences observed between all of the PPs, plain glass bottles (stored at 4 °C) seem to offer the best compromise in order to obtain good recoveries of most PPs between 7 and 28 days [61].

Nevertheless, it has been demonstrated that the use of a specific container material depends on the chemical family of the PPs [39,49,61]. Concerning antibiotics, unsilanized glass or HDPE bottles can be used to recover tetracyclines after 7 days (86–93%) without a statistically significant change [61]. It should be noted that the observed loss may be attributed more to the stability of tetracyclines than to the tested containers [61]. Satisfactory recoveries after 7 days with silanized glass bottles were obtained for approximately 71% of targeted β-lactamins, and 100% of all of the target sulfonamides and quinolones [61]. Similar results were obtained for sulfonamides in HDPE bottles, although fewer macrolides were recovered with regards to all types of bottles: only 50% and 57% of the analytes were suitably recovered after 7 days with silanized glass and HDPE bottles [61]. Plastic materials such as HDPE may contain additives that might be leached from the bottle and might cause interferences during the analysis of the PPs as observed by Vanderford et al. 2011 who used the labelled isotope standard sulfamethoxazole to correct water matrix effect [39]. Moreover, to some extent, plastic polymers might increase the degradation of organic pollutants such as PPs by forming biofilms on the bottle surface [63].

With regards to hormones and steroids, 94% of the PPs in silanized glass bottles were well recovered, whereas 100% of the analytes were recovered without a statistical change when using unsilanized glass and HDPE bottles, respectively [61]. Alternatively, another study showed that silanized glass, HDPE and unsilanized glass bottles, in decreasing order, offered the lowest mean loss of 10 free oestrogens in water solutions (the matrix origin was not mentioned) [49]. The silanization process might represent some advantages over the long term use of old glass bottles as per Suri et al. who studied this issue by comparing the recoveries of 10 oestrogens hormones between PPs stored in glass bottles that were scratched with sand-paper on their internal surface to simulate normal working wear (i.e. cleaning, washing, etc.) and PPs stored in silanized glass bottles [49]. The results ranged from a gain of 13% to a loss of 33%, with oestrone, equilin and gestoden having more than a 20% loss after 7 days. The authors assumed that the coating of the silanization agent on the glassware may create a non-polar film that covers the free silanols, possibly preventing some oestrogens from binding to the glassware. With respect to all analytes other than antibiotics and hormones, it was demonstrated in the EPA study that 26 PPs belonging to 14 different therapeutic families were recovered without a statistical change with glass bottles after 7 days of storage [6]. These results agree with those from another study that has also shown best recoveries with unsilanized glass bottles for all of the 19 PPs belonging to eight therapeutic families after 14 days of storage [39].

Therefore, these three studies have emphasized that sample containers may affect analyte recoveries. The best choice of bottle material clearly depends on the target PPs. However, for most of the target PPs (all families considered), unsilanized glass bottles seem to offer the best performances and may represent the best compromise in terms of preserving a broad variety of PPs in water samples, with the exception of some antibiotics (macrolides and

Table 2
Tests conditions to study the effect of preservatives and acidifying agents on PPs in surface water.

Analytes	Number of replicates (n)	Bottle material	Spiking concentration (ng/L)	Samples pre-treatment before storage	Storage temperature(s)	Test duration	Remark	Ref.
				Non-acidic preservative agents				
Oestriol, Oestradiol, 17 α-Ethynyloestradiol, Oestrone	2	Glass	10	Formaldehyde 1% v/v	+4 °C	28 days	–	[40]
Trimethoprim, Sulfamethoxazole, Ibuprofen, Naproxen, Diclofénac, Carbamazepine, Phenytoin, Primidone, Fluoxetine, Diazepam, Meprobamate, Gemfibrozil, Iopromide, 17 beta-Oestradiol, Progesterone, Testosterone, Oestrone, 17 α-Ethynyloestradiol, Atenolol	6	Non-silanized amber glass	n.m.	Filtration, sodium azide (1g/L)	+4 °C, +25 °C	28–35 days	–	[39]
Diclofenac, Ketoprophen, Gemfibrozil	n.m.	Amber glass	No spiking	• MeOH (5%, v/v) • Formaldehyde (5%, v/v)	+4 °C	8 days	–	[67]
Trimethoprim, Naproxen, Caffeine, Carbamazepine, Gemfibrozil, 17 beta-Oestradiol, Oestriol, Oestrone, 17 α-Ethynyloestradiol , Norgestrel, Medroxyprogesterone, 19-Norethindrone, Progesterone	3	Amber glass	100	• Filtration (0.45 μm PTFE membrane), acidification (pH 2.6) with formic acid, methanol 2.5 % (v/v)	+4 °C	21 days	–	[89]
17β-oestradiol, Oestrone, Oestriol, Zearalanol, Zearalenone, Zearalanone , Testosterone, 5α-androstan-17β-ol-3-one, Androsterone, 5α-androstane-3,17-dione, 4-androstene-3,17-dione, Boldenone, Nandrolone, 17β-trenbolone, 17α-trenbolone, Progesterone, 17,20-dihydroxyprogesterone, Melengestrol, Melengestrol acetate	3	Silanized amber glass	1000	Filtration, sodium azide (1g/L)	+4 °C	14 days	–	[64]
				Acidifying agents				
Erythromycin–H2O, Trimethoprim, Sulfamethoxazole , Triclosan, Pentoxifylline, Acetaminophen , Ibuprofen, Naproxen, Diclofenac, Caffeine, Carbamazepine, Dilantin, Hydrocodone, Fluoxetine , Diazepam, Meprobamate, Gemfibrozil, Iopromide, Progesterone, Testosterone, Oestradiol, 17 alpha-Oestradiol, Androstenedione	4	Silanized amber glass	100	Sulfuric acid (pH 2)	+4 °C	14 days	Sample filtration n.m.	[38]
Trimethoprim, Sulfamethoxazole, Ibuprofen, Naproxen, Diclofénac, Carbamazepine, Phenytoin, Primidone, Fluoxetine, Diazepam, Meprobamate, Gemfibrozil, Iopromide, 17 beta-Oestradiol, Progesterone, Testosterone, Oestrone, 17 α-Ethynyloestradiol, Atenolol	6	Non-silanized amber glass	n.m.	Sulfuric acid (pH < 2)	+4 °C, −20 °C, 25 °C	28–35 days	Sample filtration immediately prior to extraction	[39]
17 α-Ethynyloestradiol, 17 beta-Oestradiol, Oestrone	2	n.m.	10	• Filtration (0.45 mm glass fibre filters), phosphate buffer (pH 2.5–3.0)	+4 °C	7 days	Data not shown	[84]
17β-Oestradiol, Oestrone, Oestriol, Zearalanol, Zearalenone, Zearalanone , Testosterone, 5α-androstan-17β-ol-3-one, Androsterone, 5α-androstane-3,17-dione, 4-androstene-3,17-dione, Boldenone, Nandrolone, 17β-trenbolone, 17α-trenbolone, Progesterone, 17,20-dihydroxyprogesterone, Melengestrol, Melengestrol acetate	3	Silanized amber glass	1000	• Sulfuric acid (pH2) • Hydrochloric acid (pH2)	+4 °C	14 days	–	[64]

"n.m.": not mentioned.

quinolones) that are better recovered in silanized glass or HDPE bottles. For each specific set of PPs, it would be relevant to perform additional tests during the analytical development to ensure that the selected material of the sample containers does not have an influence on the PP concentrations in the natural matrix. Furthermore, it may be assumed that the presence of organic matter in natural matrices may decrease the adsorption of PPs onto the bottle surface (competition between OM and bottle surface) [61] which further underlines the needs to better understand and to determine the impact of container material on PP preservation in natural waters.

3.2.3. *Impact of temperature and holding time*

Temperature is a physical preservation technique for PPs that may ensure the efficient management of the stability duration for PPs in natural water samples. It is of prime importance to be aware of how long and at which temperature(s) PP concentrations remain unchanged before analysis to have an accurate picture of PP occurrence in water samples. The temperature at storage may impact the degradation pathways of PPs (biodegradation and other chemical transformations in general) by increasing bacterial growth and the kinetics of some chemical reactions (e.g. hydrolysis, photodegradation, etc.). Adsorption/desorption equilibriums

of PPs with OM and/or to the surface of the bottle material might also be altered and become irreversible over time. Alternatively, the freezing or refrigeration of samples may present some drawbacks, namely in that it requires maintaining the cold chain without power failure. Furthermore, when the samples are defrosted, it might produce insoluble aggregates in the water samples that clogg the filters during the filtration step and result in a possible loss of PPs in the samples [39]. Therefore, optimum temperature and time storage conditions before analysis need to be studied for a set of PPs in surface and groundwater samples. Few studies on the influence of temperature on PPs stability have been reported for some PPs in natural samples without any chemical preservative agent and stored for a variable amount of time (Table 1).

A total of 51 PPs and metabolites belonging to seven therapeutic classes have already been monitored in unpreserved surface water samples stored at various temperatures (−20 °C/−18 °C, +4 °C, and 20 °C/25 °C (i.e. room temperature (RT)) during time periods ranging from 3 to 124 days. There is still a current need to enlarge the studies to other representative PPs from these seven groups and complete them with experiments on other widespread therapeutic groups. Approximately 70% of the target PPs (i.e. 36 PPs) were reported to be stable in surface water samples stored at one temperature for at least 7 days (Fig. 2). Among these 36 PPs, 12 PPs (diazepam, phenytoin, primidone, trimethoprim, ciprofloxacin, oxolonic acid, iopromide, 17 α-Ethinyloestradiol, gemfibrozil, diclofenac, ibuprofen, and naproxen) seem to be stable during at least 8 days when stored at −20 °C, +4 °C as well as at room temperature. It is also relevant to note that room temperature conditions may be suitable for the storage of 27 PPs, thereby allowing more flexibility with regards to time and space storage when handling numerous sample bottles during a sampling campaign and analysis. According to the therapeutic family of the PPs (and to their chemical structure, by extension), there is no apparent major discrepancy between the stability of PPs kept in samples at −20 °C, +4 °C and RT, except for the hormones. A previous study emphasized the fact that only progesterone and testosterone cannot be preserved at 4 °C within a short period of time (≤3 days) eventhough the other 17 targeted PPs were stable [39]. The results of another study have emphasized that the instability of hormones kept in unpreserved surface water samples protected from light and kept at 25 °C was mainly caused by biodegradation [39,64]. Among the five target PPs, only the synthetic hormone 17 α-ethinyloestradiol resisted degradation within 35 days storage [39], which was also confirmed in Baronti et al. [40] (data not shown). The structure of 17α-ethinyloestradiol containing a 17-ethynyl substituent (unlike the other oestrogens) might explain its stability. Many steroids may undergo metabolic inter-conversion between one PP and another, as has been suggested for the conversion of oestradiol into oestrone in Vanderford et al. 2011, and may hence distort the results of the analysis [39,64]. Otherwise, freezing conditions seem more suitable to preserve hormones as only progesterone showed a severe loss in concentration after 35 days of storage at −20 °C as well as 4 °C and RT conditions. With regards the cold storage at +4 °C, the poor stability of 15 hormones (androgens, oestrogens, progestogens) within 14 days of storage versus melengestrol and melengestrol acetate, which were well recovered after 14 days, was shown in Havens et al. [64]. The 6,7 double bond and 16-methylene groups of melengestrol structures would explain its relative apparent stability whereas these substituents are not present in the structure of the other progestrogens.

The results for 17β-oestradiol and oestrone (oestrogens) are controversial between the two studies. They were found to be stable up to 28–35 days in Vanderford et al. and significantly degraded within 14 days in Haven et al. [39,64]. This difference in the data suggests that the individual composition of a water sample (microbial flora, pH, organic matter, minerals, etc.) within one study and between different studies may vary and thus may have an effect on the kinetics of PP degradation and may also result from dissimilarities found between the protocols used in the stability studies (Table 2). This hypothesis has been supported by the literature [64]. However, 17α-ethinyloestradiol is still resistant to sorption and degradation; furthermore progesterone and testosterone were unstable in surface water at +4 °C within 3–35 days in both studies [39,64].

The other differences between the results on the influence of temperature concern isolated cases of instability for six individual PPs (fluoxetine and meprobamate (antidepressants), atenolol (β-blocker), carbamazepine (anticonvulsant), sulfamethoxazole (sulfonamide antibiotic) summarized in Table 4). These results also need to be confirmed in future studies as they reveal the importance of verifying the temperature conditions in order to avoid underestimating concentrations for a multi-residual assortment of PPs in surface water samples.

With regards to groundwater samples, only two studies have reported data on the stability of 31 PPs in samples kept at +4 °C for 7 days (19, 20). According to the results, all of the PPs may be stored at +4 °C within 6 or 7 days except for furosemide (diuretic) and clotrimazole (antifungal agent), which can only be preserved for up to 4 days, and fenofibrate (lipid regulator) and bromazepam (anti-anxiety drug), which are only stable for two days in groundwater [65,66]. It would be interesting to investigate other storage temperatures so as to be able to extend the storage duration. It is also interesting to note that ketoprofen (NSAID) and gemfibrozil (lipid regulator) were stable up to 6 days in groundwater although they were reported to remain stable over 28–35 days in surface water [39]. As the mineral composition of groundwater is generally higher than in surface water [39,65], it is assumed that compounds with carboxyl or carbonyl groups in their structure (e.g. ketoprofen, gemfibrozil, or quinolones, tetracyclines, etc.) might be able to more easily bind to mineral cations (Ca^{2+}, Al^{3+}, Zn^{2+}, etc.) present in groundwater, forming weak or insoluble complexes that may be adsorbed onto the glass surface of the sample containers. This outcome strengthens the fact that instead of extrapolating stability data for PPs between matrices, as is sometimes done for instance with deionized water data liken to PPs stability in surface water [67], stability studies should be automatically monitored with natural samples, ideally with water from the selected sampling stations for each environmental field study.

It should also be mentioned that there is another relevant way to preserve samples that consists of cooling or freezing samples extracts in organic solvents or solid phase extraction (SPE) cartridges after sample loading within the shortest delay possible after sampling. This method would provide some benefits in terms of space, time and handling during analysis campaigns when the stability of the PPs in extracts have been verified during the analytical development. Only a few studies have reported data on the stability of some PPs (sulfonamides, NSAIDs, hormones) in solvents or in the solid sorbents phase in SPE cartridges directly obtained from natural water samples extraction [57,68–70]. The stability of PPs in solvent extracts or SPE cartridges were found to vary from 7 to 90 days although the results of these studies were not detailed in this review. It appears essential to investigate this issue because many experiments (even some stability studies of PPs in natural water sample bottles) include a freezing storage period for the solvent extracts in their protocol (following water sample storage and extraction) without showing consistent data on stability in the solid phase sorbents or solvent extracts [5,39,71,72].

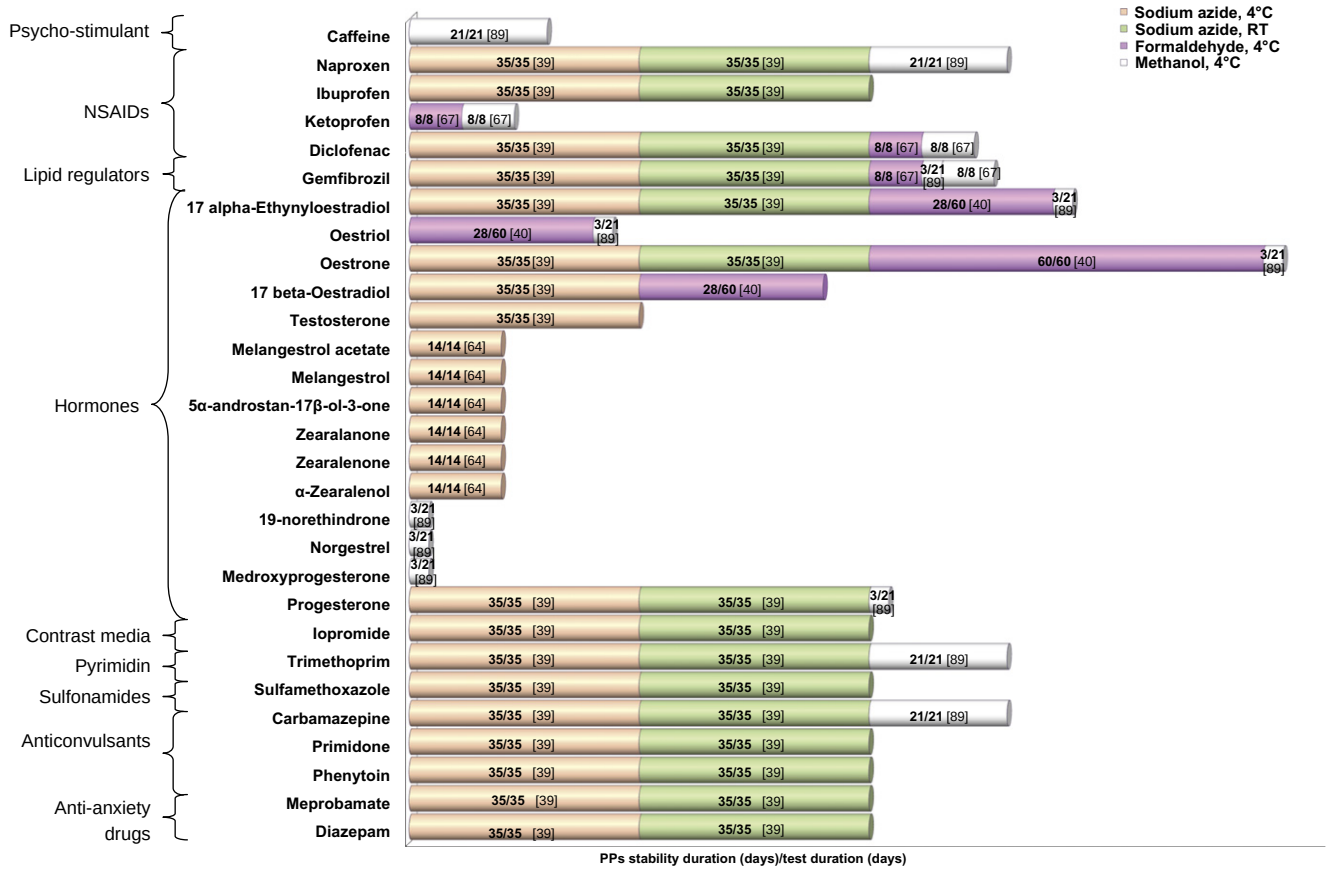

Fig. 3. Stability duration of PPs as a function of preservatives in surface water samples.

4. Impact of sample pre-treatments and preservation techniques

4.1. Filtration

PPs are mainly present in the dissolved phase of environmental waters although they may be adsorbed to suspended solids and dissolved organic matter depending on the pK_a, $\log K_{ow}$ as well as the composition and matrix proprieties of the PPs (pH, salinity, temperature, organic matter composition and content) [1,58,65]. Among the few studies that have focused on the ubiquitous presence of PPs in suspended matter and the aqueous phase of natural samples, Ferreira de Silva et al. (2011) showed that approximately 70% of the 30 target PPs were predominantly found in aqueous water with a concentration distribution in suspended matter greater than 5% [73,74]. Furthermore, 10 PPs among the 30 targeted PPs were largely found in suspended matter from a Spanish river, i.e. 10 PPs were distributed at more than 50% in the suspended matter (rather) compared to the dissolved river water [74]. Thus a filtration process before sample storage could be recommended when determining PPs exclusively in the aqueous phase of natural water. In that case, it is expected that organic matter will have to be eliminated from samples by a filtration step, even though it reduces the matrix interferences during (LC–MS) analysis [70], for two major reasons:

- to avoid possible analysis biases in PPs concentrations possibly caused by the sorption/desorption of PPs bound to particulate material in water samples,
- to potentially reduce PP biodegradation by the microbial flora drinven by OM.

Filters used to eliminate OM from water samples would represent another risk for the adsorption of PPs on its surface even though the impact of filtration on PPs in natural water samples has been invalidated by few studies [35,40,65]. The choice of appropriate filters (with regards to material and pore size) depends on its ability to release all of the targeted PPs. Glass fibre filters are widely used for filtration [5,59,75], but other type of filters are also used such as cellulose acetate membrane [17], nylon membrane [76,77], cellulose acetate and non-specified membrane filters [78]. Within the framework of an interlaboratory essay on four NSAIDS in environmental waters, Heath et al. tested the impact of filtration on surface water samples by comparing results from unfiltered and filtered samples with glass fibre filters and various membrane filters (pore size not mentioned) [70]. This evaluation proved that filtration did not have an impact on the selected NSAID concentrations in the surface water samples. These results are in agreement with another study that analyzed unfiltered/filtered (glass fibre filters, 0.7 μm) samples spiked with 26 different PPs from eight therapeutic families ($\log K_{ow}$ between −2.3 and 6.3, acidic, basic, neutral and amphoteric PPs) at 100 ng/L and suspended matter between 5 and 85 mg/L [65]. No sorption onto the filter material was observed even for the most hydrophobic PPs (e.g. clotrimazole, pK_a 6.3). Porosity also does not seem to be a key issue regarding the good recovery of the PPs in the aqueous phase of wastewater samples obtained after filtration through three glass fibre filters with different pore sizes (0.7 μm, 1.2 μm and 2.7 μm) as shown in Baker et al. [35]. The influence of filtration on PPs still

currently needs to be tested in surface and groundwater as the commonly used filters may have small pore sizes (i.e. < 0.7 μm).

To prevent PPs from degradation and desorption from OM in water samples filtration should be carried out as soon as possible after sampling. Although it is often not possible to filter the samples on-site during a sampling campaign, which would be ideal, the samples are usually vacuum-filtered immediately upon receipt at the laboratory before possible storage [5,77].

The influence of filtration on wastewater samples during 72 h of storage has been highlighted in a study reporting a longer-lasting preservation in filtered samples than in unfiltered samples for 11 PPs and 5 PPs among 35 PPs stored at 19 °C and 2 °C, respectively [35]. This study, which suggests that PPs in wastewater samples undergo less severe transformation during storage due to filtration, has to be confirmed in natural waters (i.e. surface and groundwaters).

4.2. Non-acidic preservative agents

Because some PPs are unstable at all temperature conditions, samples should be stored within the shortest time possible before analysis. It might be necessary to add chemical agents (i.e. preservatives) to the samples before storage to improve the stability of the PPs. Preservative additives might represent an alternative or a complementary technique when combined with temperature preservation. According to the preservative agents, their concentrations and the nature of the bacteria flora, preservative additives may inhibit bacterial growth in natural water samples thereby protecting PPs from biodegradation [39,64]. Some laboratories usually add preservative agents into natural water samples before sampling or rapidly after sample collection in order to improve the stability duration of PPs before pre-treatment and analysis. A few chemical agents have been previously identified for preserving PPs in natural water samples such as sodium azide, formaldehyde and methanol [40,79–81]. Sodium azide is a powerful poison that notably reacts with metal ions from bacteria enzymes or metal ions present in water, inhibiting bacteria and causing it to be toxic with respect to possible human exposure during experimental handling. Conversely, the aqueous solution of formaldehyde (called formaline) is also a biocide (bactericide, fungicide, virucide and sporicide) that may inactivates some microorganisms by alkylating the amino and sulfhydryl groups of their proteins, ribonucleic acids and deoxyribonucleic acid [82]. Methanol is an alcohol that may also have a bactericidal action in natural water although it rapidly decomposes with a half-life of a few days in surface water [63]. It is also expected that the addition of a small amount of methanol to the samples would prevent the adsorption of the PPs onto the glass surface of the sample container although there is no data supporting this hypothesis [83].

Besides the development of appropriate analytical procedures that must include measures to avoid producing interferences during analysis possibly caused by the presence of preservatives in the samples, some stability tests are especially needed to verify the influence of such agents on PPs in water during sample storage. However, only a few studies have reported data on the influence of preservatives on PPs in natural water (Table 2).

Thirthy-nine PPs covering 10 therapeutic groups (NSAIDs, hormones, anticonvulsants, anti-anxiety drugs, etc.) were studied regarding their stability in preserved surface water samples. To the best of the authors' knowledge, hormones were predominantly investigated compared to other therapeutic groups such as antibiotics, β-blockers, etc., which were poorly studied or never studied at all. Furthermore, no studies on PP preservation in groundwater samples were noticed in the literature. Among the 39 target PPs, nearly 90% of the PPs were in common with the target PPs for which the influence of temperature was also studied in unpreserved surface water samples (Fig. 3).

Among the 39 target PPs, 29 PPs seem to be stable for at least 3 days during the storage of preserved surface water samples with formaldehyde, sodium azide or methanol (Fig. 3). Fig. 3 exhibits the number of days during which the (mean) loss in the concentration for the 29 PPs was estimated to be negligible over the tested duration ranging from 3 to 60 days at 4 °C and/or at RT. Only the 10 remaining PPs (among the 39 target PPs), principally oestrogens, androgens and atenolol (β-blocker), and fluoxetine (antidepressant drug), showed a significant decrease in concentration within the tested periods (Table 4), although the longest period of stability in the preserved samples before the cut-off time for the experiments was not mentioned. Based on the reported results, the preservatives were thereby assumed to be inappropriate for preserving these 10 PPs in surface water samples. However, it is important to remind researchers to keep a critical eye on the data results since, in particular, the tested periods differ between the reviewed studies (Table 2).

On the whole, all of the stability studies showed that preservatives have no impact on the majority of the target PPs compared with their storage in unpreserved surface water samples; however, a positive impact on hormone stability has been demonstrated. Moreover, the addition of chemical preservatives into the water samples may lead to degradation reactions occurring within PPs during sample storage.

Sodium azide and formaldehyde appear to be suitable as preservatives for the major part of the PPs groups despite some exceptions for some specific PPs in the hormone group. Results from experiments with sodium azide were comparable when samples were stored at 4 °C as well at RT, with only one exception for oestradiol which was not sufficiently recovered at RT after 28–35 days of storage [39]. These results were attributed to the incapacity of sodium azide to definitely reduce the microorganisms that degrade hormones and were experimentally proved by measuring the microbial activity during the stability study [39,64]. Controversial results were found for some hormone PPs (progesterone, testosterone, 17 β-oestradiol and oestrone) which were not significantly recovered after 14 days in Havens et al. and significantly recovered in preserved surface water samples in Vanderford et al. [39,64]. The differences between the experimental procedures (see Table 2) might explain these contradictory results which would therefore need to be confirmed.

Sodium azide combined with RT has no impact on PPs, given their stability reported in unpreserved samples at RT (Fig. 2); however, it seems to prolonge the stability of progesterone and oestrone in surface water samples (Table 4, Fig. 3). Similarly, sodium azide combined with a 4 °C storage temperature may be used to greatly improve the stability of some oestrogens (zearalanol, zearalenone, zearalanone) and one androgen (5α-androstane-3,17-dione) up until 14 days although it has no impact on other PPs that may be similarly stable or degraded in unpreserved surface water samples stored at 4 °C.

Since fewer PPs were studied as regards the influence of formaldehyde and methanol in surface water samples stored at 4 °C, the reported results demonstrate that the main advantage of both preservatives is to increase the stability of oestriol compared with its poor stability in unpreserved samples and with the negative impact of sodium azide found on this PP (Table 4). However, it should be noted that Togola et al. mentioned that although formaldehyde and methanol did not have an effect on the preservation of some PPs, these two chemical agents increased the level of variability observed in the results for all experiments durations [67]. It can be assumed from Fig. 3 that methanol is appropriate to preserve NSAIDs, caffeine,

Table 3
Influence of acidification on PPs preservation in surface water samples.

Family	Analytes	H_2SO_4, pH2, 4°C	HCl, pH2, 4°C	H_2SO_4, pH<2, 4°C	H_2SO_4, pH<2, 25°C	Phosphate buffer, pH 2.5-3.0, 4°C
		7 or 14 days (n.m.) [38,64]	14 days [64]	28-35 days [39]	28-35 days [39]	7 days [84]
Anticoagulant	Pentoxifylline	=	n.d.	n.d.	n.d.	n.d.
Anticonvulsant	Carbamazepine	=	n.d.	+	=	n.d.
	Dilantin	=	n.d.	n.d.	n.d.	n.d.
	Phenytoin	n.d.	n.d.	=	=	n.d.
	Primidone	n.d.	n.d.	=	=	n.d.
Antidepressant, anti-anxiety drugs	Diazepam	=	n.d.	=	-	n.d.
	Fluoxetine	+	n.d.	=	+	n.d.
	Meprobamate	=	n.d.	=	+	n.d.
Antimicrobial agent	Triclosan	=	n.d.	n.d.	n.d.	n.d.
Contrast media	Iopromide	=	n.d.	-	-	n.d.
Homones	Testosterone	+	+	n.d.	=	n.d.
	5α-Androstane-3,17-dione	+	+	n.d.	n.d.	n.d.
	Androsterone	+	+	n.d.	n.d.	n.d.
	4-Androstene-3,17-dione	+	+	n.d.	n.d.	n.d.
	Boldenone	+	+	n.d.	n.d.	n.d.
	Nandrolone	+	+	n.d.	n.d.	n.d.
	17-β-Trenbolone	+	+	n.d.	n.d.	n.d.
	Ehtynyloestradiol	=	n.d.	=	=	n.d.
	Oestradiol	= [38] + [64]	+	=	n.d.	n.d.
	Oestrone	n.d. [38] + [64]	+	=	n.d.	n.d.
	Progesterone	+	+	+	+	n.d.
	17,20-Dihydroxyprogesterone	=	+	n.d.	n.d.	n.d.
	Melangestrol	+	+	n.d.	n.d.	n.d.
	Melangestrol acetate	+	+	n.d.	n.d.	n.d.
Lipid regulator	Gemfibrozil	=	n.d.	-	=	n.d.
Macrolide	Erythromycin-H2O	=	n.d.	n.d.	n.d.	n.d.
NSAIDs	Acetaminophen	=	n.d.	n.d.	n.d.	n.d.
	Diclofenac	=	n.d.	-	-	n.d.
	Ibuprofen	=	n.d.	-	=	n.d.
	Naproxen	=	n.d.	-	=	n.d.
Opioidanalgesics	Hydrocodone	=	n.d.	n.d.	n.d.	n.d.
Psycho-stimulant	Caffeine	=	n.d.	n.d.	n.d.	n.d.
Pyrimidin	Trimethoprim	+	n.d.	=	=	n.d.
Sulfonamide	Sulfamethoxazole	=	n.d.	-	-	n.d.
β-blocker	Atenolol	n.d.	n.d.	=	=	n.d.

trimethoprim and sulfamethoxazole between 8 and 21 days although the duration of the experiments was shorter than in other studies on preservatives. In addition, methanol has a negative impact on gemfibrozil (lipid regulator) and would not be recommended for some hormone PPs although most of these PPs were stable until 35 days in all reported unpreserved/preserved conditions (Figs. 2 and 3). Further studies are needed in order to be able to come to a conclusion regarding the relevance of using methanol as a preservative in surface water samples.

Based on the ability of some PPs to form precipitates or chelate complexes with mineral ions in natural waters [46,47], chelating agents such as ethylenediaminetetraacetic acid (EDTA) may be added to the samples. By bonding with metal cations, EDTA prevents PPs from forming complexes in water samples which may be adsorbed onto the free silanol groups present on the surface of the glass bottle. The performance of EDTA was reported in the literature regarding the increase of solid phase extraction recoveries for tetracyclins, macrolides and fluoroquinolones antibiotics in water samples following the addition of EDTA to the samples [16].

4.3. Acidifying agents

It is widely known that the reaction kinetics of degradation are considerably influenced by the pH of the matrix. Most bacteria grow optimally within a pH range between 5 and 9. Therefore, if the pH of the surface water samples is reduced, it may inhibit biological activity, as it has already been shown in the literature [64]. Therefore, it can be expected that supplemental acid agents in natural water samples would slow the biodegradation of some PPs during storage. Moreover, it can be suggested that a low pH (≤ 2) in water might prevent the adsorption of some PPs to organic matter and to the sample containers. Indeed, depending on the acido-basic proprieties (pK_a) of the PPs, acidic conditions (i.e. pH < pK_a) may lead to the shift of anionic species of some PPs present in water into their protonated PPs forms which might weaken the potential ionic interactions between PPs onto OM [34] and probably onto the sample bottle surface. Unfortunately, acidification may also cleave the conjugated forms of hormone PPs and thus result in an overestimation of the observed recoveries for the deconjugated hormone PPs, as was observed in Havens et al. [64].

Stability studies have focused on nearly 40 PPs in surface water samples under acidic preservation within 7 to 28–35 days, half of which are represented by steroid hormones [38–40,64]. However, no study has reported data on the stability of PPs in acidified groundwater samples. In combination with temperature, strong mineral acids like hydrochloride acid, sulfuric acid, and phosphate buffer were selected to evaluate their influence on PP preservation in surface water samples during storage [38–40,64]. The reviewed performances of the different acidification techniques for samples combined with temperature and stored for variable lengths of time are compiled in Table 3. In this table, different colours are used to represent the stability of the PPs within a storage period based on a limited range of a $\pm 20\%$ loss for each PP, which may be considered as stable (stable PPs in green, unstable PPs in red). Additional information is given in this table, highlighting the benefits or disadvantages of samples acidification in terms of PPs stabilization as observed through the differences between the recoveries obtained for the preserved and unpreserved surface water samples stored at the same temperature and for the same duration.

On the whole, the adjustment of surface water samples to pH 2 were found to be appropriate for the majority of the tested PPs at 4 °C although there are still some knowledge gaps for some therapeutic families, particularly for antibiotics. More precisely, the use of sulfuric acid or hydrochloric acid seems to stabilize hormone PPs, fluoxetine (antidepressant) and trimethoprim (antibiotic), whereas these molecules were not significantly recovered as well in unpreserved surface water samples at 4 °C as in surface water preserved samples with sodium azide (1 g/L) [38–40]. Acidification at pH 2 seems appropriate to prevent the degradation of hormones, fluoxetine and trimethoprim without adversely impacting the several other tested PPs (a gain in recoveries from 31% to 71%) [38,64]. Boldenone, 5α-androstane-3,17-dione, 17,20-dihydroxyprogesterone and diazepam were better stabilized under pH < 2 than in non-acidified samples but were not sufficiently preserved in samples after 14 days and 28–35 days of storage. Surface water samples adjusted to pH 2.5–3 and stored at 4 °C showed also good recoveries of oestrone, 17α-ethynyloestradiol and oestradiol after 7 days of storage at 4 °C, whereas the influence of the pH was not evaluated by the comparison with some unpreserved samples [84]. Conversely, the acidification at a lower pH (pH < 2) seems to offer more drawbacks than benefits regarding the already tested PPs in samples stored at 4 °C (Table 3).

There seems to be a negligible advantage to adjust the samples to pH < 2 as it had no impact on half of the tested PPs and in particular, only carbamazepine and progesterone were better stabilized compared to the unpreserved samples. Moreover, the major inconvenience of reducing the pH of the surface water samples is still that there is a collateral significant degradation of 6 PPs (i.e. a % loss between 20% and 50%, for diclofenac, ibuprofen, naproxen, sulfamethoxazole, iopromide, and gemfibrozil) that occurs although these PPs were found to be stable in unpreserved samples after the same duration (25–35 days) at 4 °C (see Table 4 and Fig. 2).

Given the results at pH 2 and pH < 2, the hydrolysis of the weak acidic PPs (diclofenac, ibuprofen, naproxen, and gemfibrozil, pK_a 4.1–4.9), except sulfamethoxazole (pK_a 1.6, 5.7), seems to be most favoured below pH 2. As for sulfamethoxazole, it is an amphoteric PPs that behaves as a weak acid and has propensity for producing salts under strong acidic conditions [85], hence explaining the depletion in the concentration occurring during storage. Because of the significant negative influence of pH < 2 observed for some PPs in surface water samples, depiste the fact that some of them were actually sufficiently recovered at the end of the experiments (i.e. gemfibrozil, ibuprofen, naproxen), necessary precautions must be taken to ensure the stability of these PPs before any experiment is carried out. Storing acidified samples at pH < 2 and 25 °C seems to improve the stability of several PPs compared to unpreserved samples at 25 °C (fluoxetine, meprobamate, oestradiol and progesterone, see Table 3) although there is still significant hydrolysis of the same PPs as in acidified samples stored at 4 °C (Table 4). It should be noted that atenolol appears to be deteriorated under all tested acidic and non-acidic chemical preservatives (see Table 4). Thankfully, it is still possible to efficiently stabilize this molecule in unpreserved surface water samples at 4 °C by monitoring temperature (see Fig. 2).

5. Conclusions and recommendations

Based on the literature, it appears that the preservation of PPs in natural water samples is not an effortless task as many processes (adsorption, degradation, cross-contamination, etc.) may contribute to their depletion during storage before analysis. This review has allowed a clear presentation of the main critical parameters that may affect PP stability in natural water samples: the nature of the matrix, the light, the temperature, the material of the sample container and the addition of preservatives to the samples. PPs behave differently (even for PPs belonging to the same

Table 4
Stable PPs within at least 7 days in surface water samples as a function of the storage conditions.

Therapeutic class/Molecules	Without a preservative			With preservatives						
	−20 °C	4 °C	25 °C	Sodium azide, 4 °C	Sodium azide, RT	Formaldehyde, 4 °C	MeOH, 4 °C	H_2SO_4, pH2, 4 °C	HCl, pH2, 4 °C	H_2SO_4, pH < 2, 4 °C or RT
Antibiotics										
Azithromycin	–	–	✓	–	–	–	–	–	–	–
Ciprofloxacin	✓	✓	✓	–	–	–	–	–	–	–
Clarithromycin	–	–	✓	–	–	–	–	–	–	–
Erythromycin	–	✓	✓	–	–	–	–	–	–	–
Erythromycin-H2O	–	–	✓	–	–	–	–	–	–	✓
Florfenicol	✓	–	–	–	–	–	–	–	–	–
Ofloxacin		✓	✓	–	–	–	–	–	–	–
Oxolinic Acid	✓	✓	✓	–	–	–	–	–	–	–
Roxithromycin	–	–	✓	–	–	–	–	–	–	–
Sulfadiazine	✓	0	–	–	–	–	–	–	–	–
Sulfadimethoxine	–	–	✓	–	–	–	–	–	–	–
Sulfamerazine	–	–	✓	–	–	–	–	–	–	–
Sulfamethazine	–	–	✓	–	–	–	–	–	–	–
Sulfamethizole	–	–	✓	–	–	–	–	–	–	–
Sulfamethoxazole	0	✓	✓	✓	✓	–	–	–	–	0
Sulfapyridine	–	–	✓	–	–	–	–	–	–	–
Sulfathiazole	–	–	✓	–	–	–	–	–	–	–
Trimethoprim	✓	*	✓	✓	✓	–	✓	✓	–	✓
Anticonvulsant drugs										
Carbamazepine	0	✓	✓	✓	✓	–	✓	–	–	✓
Phenytoin	✓	✓	✓	✓	✓	–	–	–	–	✓
Primidone	✓	✓	✓	✓	✓	–	–	–	–	✓
Antimicrobial agent										
Triclosan	–	–	–	–	–	–	–	–	–	✓
Anxiolytics-antidepressant										
Diazepam	✓	✓	✓	✓	✓	–	–	0	–	✓
Fluoxetine	0	✓ (3days)	0	0	0	–	–	✓	–	✓
Meprobamate	0	✓	✓	✓	✓	–	–	–	–	✓
Contrast agents										
Iopromide	✓	✓	✓	✓	✓	–	–	–	–	0

Therapeutic class/Molecules	Without a preservative			With preservatives						
	−20 °C	+4 °C	+25 °C	Sodium azide, 4 °C	Sodium azide, RT	Formaldehyde, +4 °C	MeOH, +4 °C	H_2SO_4, pH2, +4 °C	HCl, pH2, +4 °C	H_2SO_4, pH < 2, +4 °C or RT
Hormones										
17 α-Oestradiol	–	0	–	–	0	–	0 (< 3days)	✓	✓	–
17 α-Ethynyloestradiol	✓	✓	✓	✓	✓	✓	✓ (3days)	✓	–	✓
17 β-Oestradiol	✓	0	0	*	0	✓	0 (< 3days)	✓	✓	✓
17,20-Dihydroxy-progesterone	–	0	–	0	–	–	–	0	0	–
17α-Trenbolone	–	0	–	0	–	–	–	✓	–	–
17β-Trenbolone	–	0	–	0	–	–	–	✓	✓	–
19-norethindrone	–	–	–	–	–	–	✓ (3days)	–	–	–
4-Androstene-3,17-dione	–	0	–	0	–	–	–	✓	✓	–
5α-androstan-17β-ol-3-one	–	–	–	0	–	–	–	0	✓	–
5a-androstane-3,17-dione	–	0	–	✓	–	–	–	0	✓	–
Androsterone	–	0	–	0	–	–	–	✓	✓	–
Boldenone	–	0	–	0	–	–	–	0	0	–
Oestriol	–	0	–	0	–	✓	✓ (3days)	✓	✓	
Oestrone	✓	*	0	*	✓	✓	✓ (3days)	✓	✓	✓
Medroxyprogesterone	–	–	–	–	–	–	✓ (3days)	–	–	–
Melengestrol	–	✓	–	✓	–	–	–	✓	✓	–
Melengestrol acetate	–	✓	–	✓	–	–	–	✓	✓	–
Nandrolone	–	0	–	0	–	–	–	✓	✓	–
Norgestrel/levonorgestrel	–	–	–	–	–	–	✓ (3days)	–	–	–
Progesterone	0	0 (< 3days)	0	*	✓	–	✓ (3days)	✓	✓	✓
Testosterone	✓	0 (< 3days)	0	*	0	–	–	✓	✓	✓
Zearalenol	–	0	–	✓	–	–	–	0	0	–
Zearalanone	–	0	–	✓	–	–	–	✓	✓	–
Zearalenone	–	0	–	✓	–	–	–	✓	✓	–
Lipid regulators										
Gemfibrozil	✓	✓	✓	✓	✓	✓	✓	–	–	✓
NSAIDs										
Acetaminophen	–	–	–		–	–	–	0	–	✓
Diclofenac	✓	✓	✓	✓	✓	✓	✓	–	–	0
Ibuprofen	✓	✓	✓	✓	✓	–	–	0	–	✓
Ketoprofen	–	✓	–	–	–	✓	✓	–	–	–
Naproxen	✓	✓	✓	✓	✓	–	✓	–	–	–
Psycho-stimulant										
Caffeine	–	–	–	–	–	–	✓	0	–	✓
B_Blockers										
Atenolol	0	✓	0	0	0	–	–	–	–	0

RT : room temperature
"✓": condition for which the molecule is stable during at least 7 days,
"0": unstable molecule over the duration of the stability test,
"–": not determined,
"*": controversial data that would need to be verified by additional experiments.

therapeutic class) regarding their stability under these different parameters, which demonstrates that a combination of compromises have to be decided upon and tested in order to reliably analyse various classes of PPs. Because it is often logistically impossible to handle the sampling and the analysis of numerous samples within the same day, some preservation techniques have been identified in order to resolve the difficulties encountered from sampling up to the analysis of numerous samples within the same day. Thankfully, all 58 of the reviewed PPs in this review may be successfully stabilized for 7 days in surface waters by at least one appropriate methodology with regards to temperature, acidic and non-acidic preservatives parameters summarized in Table 4. In addition, 27 PPs from 31 PPs may be preserved at 4 °C in groundwater samples for almost 6 or 7 days.

Based on the reported results from the literature, useful recommendations for accurate analysis may be pointed out. As a general rule, field investigators should follow basic precautions such as the use of amber bottles to collect samples and the storage of samples in a dark area to prevent PPs from light exposure from transport up to the analysis step. In addition, samples should be filtered as soon as possible after sampling because degradations could potentially occur in the PPs whereas this has not yet been studied in surface water and groundwater (it has only been proven in wastewaters).

This review highlights that all types (material and porosity) of filters seem to be convenient to remove the suspended matter from surface water without the apparent risk of eliminating the PPs during filtration.

Sample containers need to be clean in order to prevent cross-contamination. As for the choice of container material, since to date no tests have been carried out with natural waters, the best compromise available for all of the PP families, except for some antibiotics which are better preserved in silanized bottles or HDPE, seems to be to use unsilanized glass bottles.

Temperature is the most studied parameter that may efficiently preserve the majority of the reviewed PPs during at least one week by cooling, freezing, or even storing surface water samples at ambient temperature (Table 4). However, it remains impossible to universally preserve all PPs at the same temperature. Besides, further knowledge about the stability of PPs in the different types of water samples such as groundwaters is still needed. The storage of PPs in organic solvents from the extracted samples within a short time delay after sampling has been suggested as a relevant way to preserve some PPs until analysis. However, less is known about this alternative and additional studies are needed.

When temperature is not a sufficient preservation parameter for some PPs (especially hormones, and fluoxetine (an antidepressant)), its combination with the addition of chemical agents into samples may prolonge the integrity of PPs during storage in surface water. Sodium azide and formaldehyde seem to perform well; in addition, they prolong the stability of a few hormones and have no impact on most other PPs. However, a better influence on a wider range of hormone PPs was observed when the pH of the water samples was reduced at 2 with hydrochloric acid or sulfuric acid because they are better at microbial inhibition since microbial activity was shown to contribute toward the degradation of the PPs in the samples. Otherwise, acidic and non-acidic agents are capable of degrading some PPs that were well recovered in unpreserved samples.

Therefore, within the framework of a multiresiduals analysis, it appears quite complex to find the best compromise to preserve a wide variety of PPs in samples. This review highlights the evident need to assess the stability of PPs during the storage of natural water samples and to define the best available techniques to preserve the integrity of the analytes in all types of environmental aqueous samples. Nevertheless, stability studies have to be developed to accommodate a larger set of other representative PPs, including the veterinary drugs for which stability in natural water samples has hardly been studied so far. Presently, efforts converge on the prioritization of PPs according to their potential risk to human and ecological health. It would be easier to focus investigations into sample preservation on a set of the most relevant PPs if a priority list was provided; this way, efforts on this task would be better pinpointed. Moreover, it is also necessary to better investigate groundwater matrices with regards to the issue of PP stability.

Concerning the methodology of stability studies, there is a strong need to use standard protocols to assess and compare the stability of PPs in environmental water matrices during storage as well as during analytical preparation or analysis (European criteria 2002/657/EC). Since systematic stability-indicating tests are required to determine the expiration date of a formulated drug before its sale on the market, the design of stability studies should rigorously take into account all critical parameters that might impact the concentration of PPs over time. Further developments in preservation techniques optimizing the stability of PPs in natural water samples would greatly contribute toward the general analytical efforts undertaken to provide the best meaningful data of PP concentrations in environmental waters.

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