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Research article

Occurrence and fate of pharmaceuticals in a wastewater treatment plant from southeast of Spain and risk assessment

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ABSTRACT

Pharmaceutical and personal care products (PPCPs) can be incorporated into ecosystems and pose potential environmental and health hazards. These pollutants are becoming omnipresent in the environment because they are introduced by several sources, being particularly important the contribution of human-derived pharmaceuticals. The presence of PPCPs in waters has received increasing attention in recent years, resulting in great concern regarding their occurrence, transformation, fate and environmental risk. For that reason, the pharmaceuticals carbamazepine (CBZ), diclofenac (DIC), ibuprofen (IBU), ketoprofen (KET) and naproxen (NPX) were measured in the waters and sludge of several parts of a double step activated sludge wastewater treatment plant (WWTP) from Murcia (Spain). With these results, the biological degradation constant, the sorption coefficient and the pharmaceutical removal were calculated. Possible risks to humans and ecosystems were also evaluated.

These showed good degradation of IBU and NPX (74.4 and 84.9%, respectively), while CBZ didn't display any degradation. DIC was the compound most likely to be sorbed into the sludge (3.09 L kg^{-1}). The PPCPs removal in this double stage WWTP was compared to a previous data obtained in a WWTP of the same region with an activated sludge (single biological batch reactor). The results showed a decrease in the removal of the double stage plant, probably due to the lower hydraulic retention time employed. The study of the human and ecological risk quotients indicates a low risk of the selected pharmaceuticals (RQ < 0.1).

1. Introduction

The PPCPs constitute a diverse group of chemical products that cover human and veterinary drugs, hormones and other products used in the formulation of cosmetics, their metabolites and their transformation products. PPCPs have been found in an extensive variety of environmental samples - comprising wastewater and surface, ground and drinking water (Blum et al., 2017; Yang et al., 2017a) as well as in sludge and sediments (Huber et al., 2016). They can enter waters in different ways: by direct discharge into surface water by industries, hospitals, households and wastewater treatment plants (WWTPs) or through land runoff in the case of biosolids spread on agricultural land, reaching the groundwater by leaching or bank filtration. PPCPs can also pass into soil and sediments by irrigation with treated or untreated wastewater (Ma et al., 2018) or can be transferred to the soil by atmospheric wet deposition (Ferrey et al., 2018). Once in the soil, PPCPs and other contaminants can be absorbed by a variety of binding sites (Kaestner et al., 2014), but also can be leached to the ground waters or translocated to crops (Hurtado et al., 2016). For that reason, it is primordial to remove these pollutants before they reach the ecosystem.

The main problem with the PPCPs is that although their concentrations in the waters are generally very low (micrograms or nanograms per litre), they can still affect ecosystem balance and water quality, and even impact the drinking water resources (Yang et al., 2017a). In order to eliminate the potential risk of these contaminants, it seems to be necessary to remove the PPCPs before they reach the environment. The best way to achieve this is their removal in WWTPs.

WWTPs are able to remove or degrade some of the PPCPs found in wastewater (Martínez-Alcalá et al., 2017), although their removal efficiency changes greatly depending on the substance's physicochemical properties as well as the WWTP system and its operational parameters, such as hydraulic retention time, sludge retention time, dissolved oxygen concentration, temperature and pH (Grandclément et al., 2017). Conventional activated sludge (CAS) systems consist of the addition of microorganisms and pre-treated wastewater, with the main aims being to eliminate nutrients from the waters and to oxidize nitrogenous and carbonaceous biological matter (Grandclément et al., 2017). As such,

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Abbreviations list

BOD_5	biological oxygen demand;
CAS	conventional activated sludge
CBZ	carbamazepine;
COD	chemical oxygen demand;
DIC	diclofenac
DO	dissolved oxygen
DWEL	drinking water equivalent level
ERQ	ecological risk quotient
HLB	hydrophilic lipophilic balance
HRQ	human risk quotient
HRT	hydraulic retention time;
IBU	ibuprofen
K_{biol}	biodegradation coefficient
K_d	sorption constant
KET	ketoprofen
K_{oc}	octanol–water partitioning coefficient
K_{oc}	organic carbon-based coefficient
K_{ow}	octanol–water partitioning coefficient
MCR	maximum cumulative ratio
MDL	method detection limits
MEC	measured concentration in the effluent
MLSS	mixed liquor suspended solids
MQL	method quantification limits
MTBE	methyl tert-butyl ether
NPX	naproxen
NSAID	non-steroidal anti-inflammatory drug
pK_a	dissociation constants
PNEC	predicted no effect concentration
PPCP	personal care product
RQ	risk quotient
SPE	solid phase extraction
SRT	sludge retention time;
TSS	total suspended solids
UPLC	ultra-performance liquid chromatography
WWTP	wastewater treatment plant

the CAS process can be retrofitted into a two-stage system known as A-B process. In A-B process, A-stage is specifically designed to maximize the capture of organic matters from domestic wastewater for direct anaerobic digestion prior to biological oxidation, whereas B-stage is mainly dedicated to handling nutrients.

During activated sludge treatment in conventional WWTPs, sorption onto sludge flocs, microbial processes and volatilisation (mainly during aeration) are three main methods to degrade PPCPs. Nevertheless, the last of these can be considered negligible for the majority of PPCPs, because of the Henry's constant value of such molecules (Joss et al., 2006). Microbial biodegradation is considered as the most important removal/degradation mechanism for pollutants, and has many advantages, like low cost and undemanding operational conditions. Microorganisms are able to remove the PPCPs by using the pollutants for metabolic functions and, in some cases, different kinds of microorganisms can cooperate to remove the pollutants. For example, the nitrification process, which occurs in the aerated tank, leads to the conversion of ammonia to nitrate by nitrifying microorganisms, for example ammonia-oxidising bacteria, which could possibly oxidize PPCPs co-metabolically, improving their removal (Margot et al., 2016).

Moreover, for some lipophilic PPCPs, like musk fragrances, the adsorption onto activated sludge flocs could be a significant pathway in CAS systems (Carballa et al., 2008). However, other kinds of PPCPs (neutral or acidic), such as the pharmaceuticals CBZ, DCC, IBU, KET and NPX, seem not to be removed very efficiently from the sludge. The sludge reused in the WWTPs reflects that some pharmaceutical compounds can be sorbed into the solids could be recycled next to them in the sludge treatment line. Those compounds include both high sorption properties and low K_d values (Carballa et al., 2008). The organic carbon-based coefficient (K_{oc}) and the octanol–water partitioning coefficient (K_{ow}) of each pharmaceutical compound was determined by some approaches in order to find the connection between solids and a given compound. Nevertheless, although these expectations are reasonable talking about non-specific lipophilic interactions with other compounds, significant deviations of K_{oc} and K_{ow} coefficients were discovered regarding of PPCPs by another studies (Carballa et al., 2008). Berthod et al. (2017) showed that the hydrophobicity (log K_{ow}) was not valid for the prediction of the sorption of PPCPs to sludge. Besides, pollutants in aqueous solution with a particular pH (depending on their pK_a (dissociation constants)) will partially be in their ionic form, then, due to log$D$ (or the effective hydrophobicity) is pH-dependent, log D values are key factors to consider in the removal of such pollutants by sorption into the sludge (Tadkaew et al., 2010).

An extensive literature can be found concerning the removal of pharmaceuticals from waters. According to Verlicchi et al. (2012), CAS systems give rise to a wide range of removal efficiencies, some pharmaceuticals being very well removed (>90%) from the influent whereas others are poorly removed. During experiments in the aerobic batch, a negative mass balance for CBZ and other pharmaceutical compounds was observed by Blair et al. (2015), for which both, the sorbed and soluble pharmaceutical concentrations, were higher over time. This poor elimination of some pharmaceutical compounds can be due to several reasons: Göbel et al. (2007) hypothesised that pharmaceutical compounds could be enclosed in faecal particles and after all process, faeces are broken down by microorganisms and then, they are liberated in the liquid phase. Other authors (Kruglova et al., 2014; Verlicchi et al., 2012) proposed that in the WWTPs, the microbial activity or hydrolysis process during the treatment, could have transformed back pharmaceutical metabolites or their conjugates into the parent compounds. It seems that the combination of all processes described previously could explain the negative mass balance of some compounds (Blair et al., 2015).

Pharmaceutical compounds including DIC, IBU and NPX can be removed very well from the WWTPs, with removal efficiencies higher than 80% (Martínez-Alcalá et al., 2017), although in some studies the efficiencies were between 21.8 and 99.1% (Radjenović et al., 2009). The chemical composition of raw water, the biological structure of sludge and the different type of the treatment configuration which can be used in the CAS system (like HRT (hydraulic retention time), SRT (sludge retention time) or solid phase concentration) are parameters that could explain the differences between studies about the removal efficiencies. According to Bulloch et al. (2015), when a WWTP has a tertiary treatment, the PPCPs parental concentration in their effluents is lower than in WWTPs only with secondary treatment.

This is the first time that the pharmaceuticals are measured though a double step activated sludge WWTP in Murcia Region. The research hypothesis is if the double step in the WWTP can be an improvement regarding to other conventional WWTPs for the pharmaceuticals removal. The objective of the current paper is to determine the changes in the concentrations of pharmaceutical compounds during their passage through the WWTP and to calculate the biodegradation coefficient (K_{biol}) in the biological reactor and the sorption constant (K_d) for the selected pharmaceuticals in the sludge. The results will be part of the basis of a feasible tool to evaluate the fate and removal of pharmaceuticals during WWTP treatment. Moreover, in order to know about the real danger that these compounds can have for both the environment and the population's health, the risk assessment was made.

2. Materials and methods

2.1. Sampling site

Samples were taken from the Alcantarilla WWTP in Murcia Region, Spain (Fig. 1). This WWTP has an active sludge - double stage (A-B) treatment with coagulation, flocculation, a sand filter and ultraviolet disinfection. As can be observed (Fig. 2), this WWTP, like some of plants in the region of Murcia, has tertiary treatment and disinfection. It serves a population of 40,619 inhabitants and has a capacity of 4,745,000 m^3 $year^{-1}$. Its coordinates (ETRS89) are UTMX: 654686 and UTMY: 4199203. The efficiencies in the elimination of the total suspended solids (TSS), chemical oxygen demand (COD) and biological oxygen demand (BOD_5) during the WWTP processes were higher than 96.3% and the effluent is used mainly for irrigation purposes. The total HRT during the study was 54.4 h and the biological HRT was 20 h. The sampling campaign was in November 2017 (from the 6th to the 9th), and individual samples were taken following the total HRT of the WWTP. The pH, dissolved oxygen (DO), Eh, temperature, mixed liquor suspended solids (MLSS), TSS, COD and BOD_5 were measured during the sampling campaign and can be observed in Table S1. Samples from waters and sludge were obtained from the different sampling points: influent water and samples from the biological reactor of stage A (B.R.A. (aerobic)), different parts of the biological reactor of stage B (B.R.B1 (anoxic), B.R.B2 (aerobic), B.R.B3 (aerobic)), the effluent and the dehydrated sludge (Fig. 2).

The characterisation of the floccules indicated that they had a medium consistency with an open and irregular structure, with low abundance of filaments. The analysis under the microscope revealed a large amount of thecamoebians, indicative of a good nitrification process, low organic loads.

2.2. Pharmaceuticals analysis

In this work, several pharmaceutical compounds were selected for their study in the waters and sludge of the WWTP. The anticonvulsant/anti-epileptic carbamazepine and four nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, ketoprofen and naproxen were chosen for the study. The most relevant characteristics of these pharmaceuticals regarding to chemical properties influencing the environmental persistence and bioaccumulation of compounds, are displayed in Table 1. Where it can be observed that the highest hydrophobicity (logarithm of the octanol-water partition coefficient) is for DIC, while CBZ is the most hydrophilic compound. In the case of the dissociation constants, within a typical pH range present in the WWTPs (pH 5–9), the highest value is for CBZ, which is neutral while DIC, IBU, KET and NPX present lower values, indicating that can become negatively charged if the pH of the solution exceeds their pK_a value (Tadkaew et al., 2010). Table S2 shows the limits of detection (MDL) and quantification (MQL) and the concentration recoveries of the method.

2.2.1. Water samples

Samples were collected in 1-L amber glass bottles and were kept on ice and taken to the laboratory. Immediately, they were adjusted to pH 2 with concentrated formic acid and stored at 4 °C until extraction. Samples were extracted within 1 day of collection.

For the solid-phase extraction (SPE), we used 60 mg hydrophilic-lipophilic balance (HLB) cartridges (Oasis, Dublin, Ireland). The SPE cartridges were sequentially pre-conditioned with 5 mL of methyl tert-butyl ether (MTBE), 5 mL of methanol and 5 mL of reagent water. Due to the high organic matter content of the influent wastewater, 500 mL of the influent and reactor A samples were used, to avoid the blockage of the cartridges; for the other samples, 1000 mL were used. The first of the three replicate samples was spiked with 50 ng mL^{-1} of isotopically-labelled internal standards ([D_{10}]-carbamazepine, [$13C_6$]-diclofenac, [D-$_3$]-ibuprofen). The samples were then loaded onto the cartridges at approximately 15 mL min^{-1}, after which the cartridges were rinsed with 5 mL of reagent water and then dried under vacuum. Next, the cartridges were eluted with 5 mL of 10/90 (v/v) methanol/MTBE followed by 5 mL of methanol, into 15 mL calibrated centrifuge tubes. The resulting extract was evaporated to dryness under vacuum at 40–50 °C, using a TurboVap LV concentrator. Then, the second of the three replicate samples was spiked with 50 ng mL^{-1} of surrogate standards ([D_{10}]-carbamazepine, [$13C_6$]-diclofenac, [D-$_3$]-ibuprofen), and all the extracts were brought to a final volume of 1 mL using methanol.

Finally, all samples were passed through a 0.45 μm nylon filter before instrumental analysis in a Waters UPLC Acquity I-Class System. The liquid chromatography analysis and quality control are explained in

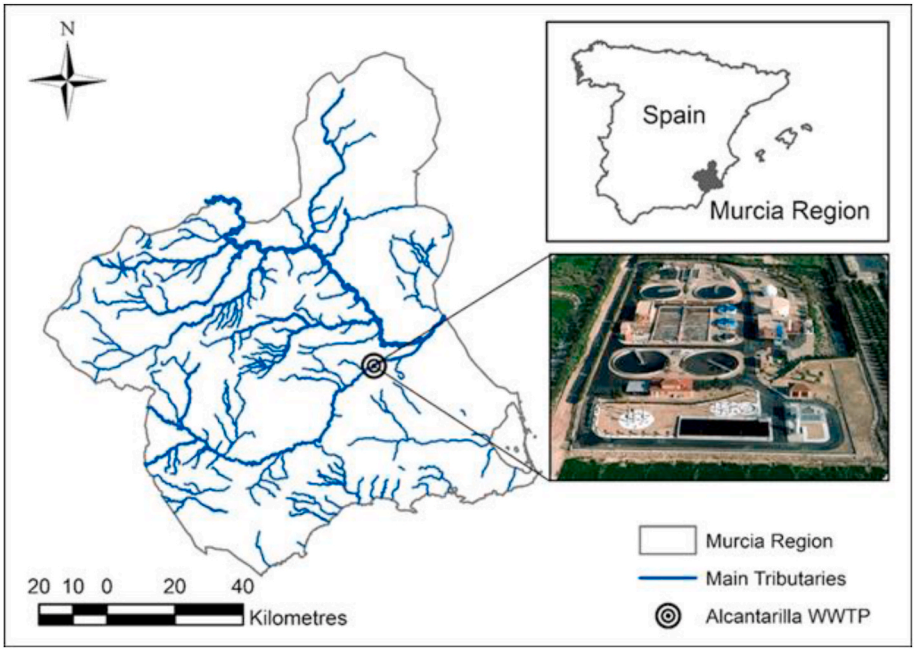

Fig. 1. Location and image of the WWTP used in the study.

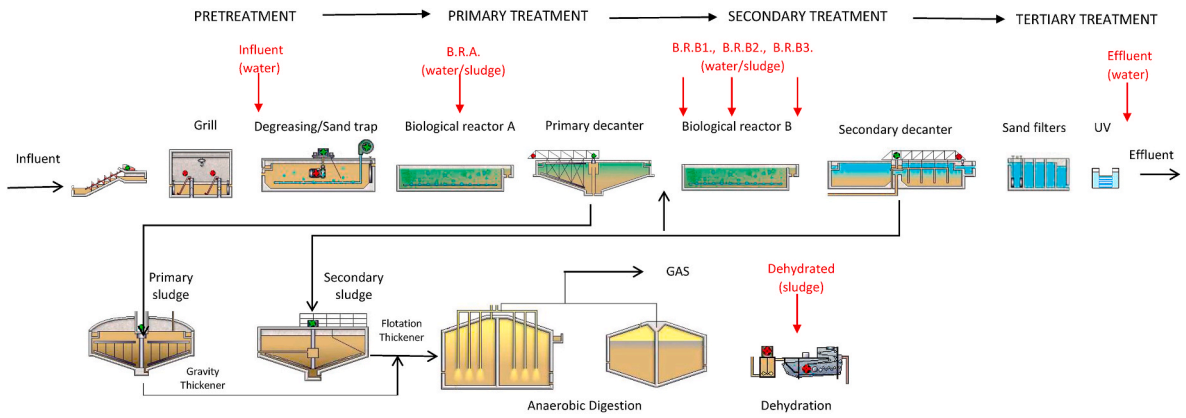

Fig. 2. Sampling points and type of sample (water and/or sludge) taken.

Table 1
Main characteristics of the selected pharmaceutical compounds. Chemical Abstract Service (CAS) registry number, logarithm of the octanol-water partition coefficient (LogK_{ow}) and dissociation constants (pK_a).

Pharmaceutical	CAS N°	LogK_{ow} (25 °C)	pK_a
CBZ	298464	2.45[a]	<1–13.9[b]
DIC	15307865	4.51[a]	4.15–4.18[b c]
IBU	51146566	3.97[a]	4.41–5.20[b c]
KET	22071154	3.12[a]	4.23[c]
NPX	22204531	3.18[a]	4.20[b c]

[a] Palma et al. (2020).
[b] Carballa et al. (2008).
[c] Araujo et al. (2014).

more detail in the supplementary material.

2.2.2. Sludge samples

For the pharmaceutical analysis of the sludge, samples were lyophilised (Christ Alpha 1–2 LD plus freeze dryer) and then homogenised using a glass mortar. The extraction was performed using the methodology of Martínez-Alcalá et al. (2017). Briefly, aliquots of 1.00 g of lyophilised sludge and 2.00 g of lyophilised dehydrated sludge were extracted sequentially with 5 and then 2 mL of methanol and then 2 mL of acetone. The supernatants obtained from each extraction step were evaporated to 0.2 mL under a nitrogen stream. Each extract was diluted to 250 mL with deionised water acidified to pH 2 with formic acid. The SPE cartridges were conditioned with 3 mL of acetone, 3 mL of methanol and 3 mL of deionised water acidified to pH 2 with formic acid, at a flow rate of about 3 mL min^{-1}. The first of the three replicate samples was spiked with 50 ng mL^{-1} of isotopically-labelled internal standards ([D_{10}]-carbamazepine, [$13C_6$]-diclofenac, [D-3]-ibuprofen). The samples were percolated through the cartridges at a flow rate of about 15 mL min^{-1}, using a vacuum manifold system (Waters) connected to a vacuum pump. The loaded cartridges were then rinsed with 6 mL of water/methanol (95:5 v/v), and 3 mL of n-hexane were used for cartridge rinsing at a flow rate of about 1 mL min^{-1}. The elution was performed with three aliquots of 1 mL of acetone, at a flow rate of about 1 mL min^{-1}. The combined aliquots were evaporated to dryness by a gentle nitrogen stream. Then, the second of the three replicate samples was spiked with 50 ng mL^{-1} of isotopically-labelled internal standards ([D_{10}]-carbamazepine, [$13C_6$]-diclofenac, [D-3]-ibuprofen), and all the extracts were brought to a final volume of 1 mL using methanol. Finally, all samples were passed through a 0.45 μm nylon filter before instrumental analysis in a Waters UPLC Acquity I-Class System. All the analyses were performed using a UPLC Acquity I-Class System and HR-QTOF-MS maXis Series (Daltonik GmbH, Bruker, Germany). For each type of water and sludge sample, recoveries were determined by comparing one replicate of the samples spiked before the SPE procedure and another spiked after the SPE procedure, with quantification by internal standard calibration (Martínez-Alcalá et al., 2017).

2.3. Equations of the biodegradation performance and sorption coefficient

Pseudo first-order biodegradation rate constants, K_{biol}, of CBZ, DIC and KET (parental compounds) were calculated as the relative amount degraded in the WWTP, according to equation (1) (Ternes et al., 2004).

$$dS_t/dt = -K_{biol}\ \mathrm{MLSS}\ S_e \quad (1)$$

Where S_t is the concentration of the drug in the water in each of the zones of the biological reactor (ng L^{-1}), t is the time (h), K_{biol} is the biological degradation constant (L g $MLSS^{-1}$ d^{-1}), MLSS is the concentration of suspended solids (average daily g L^{-1}) and S_e is the concentration of the drug in the effluent (ng L^{-1}). This equation serves to describe the exponential degradation of PPCPs, taking into account the concentration in the suspended solids of the mixed liquor. In addition, it allows us to predict the rates of removal of these compounds, depending on the configuration of the biological reactor.

The K_{biol} values are obtained by means of a regression equation, using the negative slope of the natural logarithm of the initial concentration of the drug, divided by the concentration in each one of the parts of the biological reactor, setting the intersection to zero. The K_{biol} values are based on the loss of the parent compound. For the calculation of K_{biol}, the values in Table S2 were used for those compounds whose concentrations were below the MDL.

Calculation of the sorption coefficient K_d serves to evaluate the degree of sorption of the PPCPs in the sludge (Equation (2)). The partition coefficient (K_d) is typically defined for equilibrium conditions in a batch reactor (Berthod et al., 2017) as:

$$K_d = \mathrm{PPCP}_{\mathrm{sludge}} / \mathrm{PPCP}_{\mathrm{aqueous}} \quad (2)$$

where K_d is the pharmaceutical partition coefficient (L kg^{-1}), $[\mathrm{PPCP}]_{\mathrm{sludge}}$ is the concentration of the sorbed compound expressed per unit mass (ng kg^{-1}) and $[\mathrm{PPCP}]_{\mathrm{aqueous}}$ is the concentration of the soluble compound (ng L^{-1}).

The samples chosen for this calculation were those obtained in the biological reactor B2 (aerobic zone), because the data for this section were more complete. Some authors assume that the degree of partitioning of pharmaceutical compounds between sludge and aqueous phases can be used as an indicator of their environmental fate and the risk associated with sludge disposal on land (Berthod et al., 2014).

2.4. Estimation of human and ecological risk quotients

Although the final destination of the treated water in the WWTP is

not to be consumed directly by population and although it is normally reused for agriculture production or discharged to nearby receiving rivers, in this case, is important to verify that there is no risk for possible direct consumption in terms of the analysed pharmaceutical compounds. To evaluate the pharmaceuticals that are able to produce a higher human and/or environmental risk in the WWTP effluents, were calculated two risk quotient optimised approaches (RQ).

The human age-dependent risk quotient (HRQ) for each pharmaceutical compound was calculated following the methodology of Sharma et al. (2019), dividing the maximum measured concentration in the wastewater effluent (MEC) by the corresponding age-dependent drinking water equivalent level (DWEL) (Equation (3)).

$$HRQ = MEC/DWEL \quad (3)$$

The DWEL consider factors like the acceptable daily intake or the risk specific dose for non-carcinogenic and carcinogenic effects of each pharmaceutical, the median body weight (kg) and the daily drinking water intake, of age-specific groups, the gastrointestinal absorption rate and the frequency of exposure. More information about the DWEL calculation can be found in Sharma et al. (2019). In this study were calculated the HRQ based on the DWEL calculation for babies, teenagers and adults (Table 2).

According to Yang et al. (2017b) when the HRQ value is above 1, indicate the possibility of human health risk, values between 0.2 and 1 indicate the necessity of evaluate the case with more details, while HRQ under 0.2 is considered of no appreciable concern to human health.

The possible effects against the environment was calculated following the methodology described by Hernando et al. (2006), where the ecological risk quotient (ERQ) is the ratio between the MEC and the PNEC (predicted no effect concentration) (Equation (4)).

$$ERQ = MEC/PNEC \quad (4)$$

In this study were calculated the ERQ based on the PNEC calculation for three different trophic levels (algae, crustacean and fish) adjusted by an assessment factor (AF 1000) to overcome the uncertainty of this conservative approach. The used PNEC can be observed in Table 2.

Ecological risk quotient was classified into three categories (Hernando et al., 2006): high ecological risk for values equal or above 1, moderate risk when it is between 0.1 and 1 and low ecological risk when the result is lower to 0.1. It must be considered that this RQs were calculated with the pharmaceutical concentrations found in the WWTP effluent, nevertheless a PPCPs change during the water reused or discharged processes that it was not consider in this calculation could happen.

These results consider the RQs for each single compound, nevertheless, from an ecological perspective, it should be taken into consideration that compounds occur in nature as mixtures rather than separately. For that reason, the maximum cumulative ratio (MCR) was calculated (Holmes et al., 2018) (Equation (5)).

$$MCR = \sum_{RQs} / {}_{RQmax} \quad (5)$$

In this method, the MCR is given by the sum of individual RQ values for each chemical (RQs) in the mixture divided by the maximum RQ within that mixture. In this case, MCR was classified into three categories (Holmes et al., 2018): Combinations of group I, are of concern because it includes mixtures where one or more pharmaceutical have an individual RQ > 1. Combinations of group II includes mixtures where $\sum RQ < 1$, and consequently these exposures are of low concern. Combinations of group III includes mixtures where $\sum RQ$ is > 1 only by adding up the pharmaceuticals; but no individual pharmaceutical has RQ > 1. This group is separate in two groups: IIIA, where MCR is < 2, so the majority of the toxicity is from one pharmaceutical; and IIIB, where MCR is > 2; so, in this case, the toxicity is not dominated by a single pharmaceutical.

3. Results and discussion

3.1. Concentrations in water and sludge

The concentrations of pharmaceutical compounds in water and sludge were analysed in the different compartments of a WWTP from Murcia (Spain). Results for KET are not shown, because no concentrations above the method detection or quantification limits (see Table S2) were found in water or sludge.

Samples of influent water and samples from the biological reactor of stage A (B.R.A.), different parts of the biological reactor of stage B (B.R. B1, B.R.B2, B.R.B3), and the effluent, were analysed to give a more detailed perspective on the degradation processes of the pharmaceutical compounds studied throughout the WWTP (Fig. 3).

The results obtained for water show that the antiepileptic carbamazepine was detected after the first aerobic phase of the reactor B (B1). The concentrations detected in the effluent of the WWTP (97.7 ± 7.51 ng L^{-1}) were similar to those found by Afonso-Olivares et al. (2017) and were higher than the values detected in the influent of the WWTP (not detected). This is the most typical behaviour of this pharmaceutical compound; that is, with a higher concentration in the effluent than in the influent (Nivala et al., 2019). Carbamazepine is known to be persistent

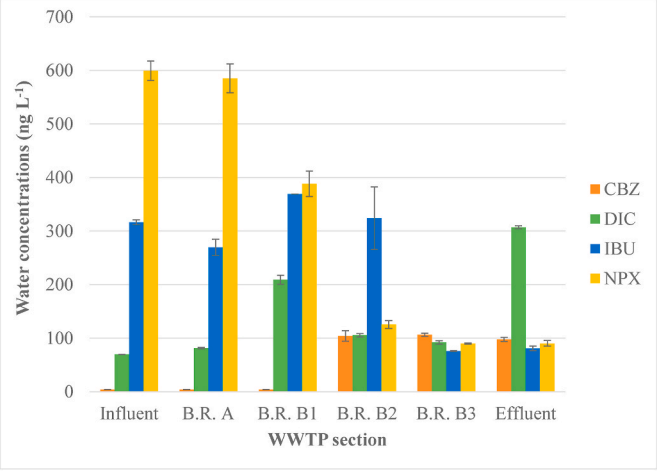

Fig. 3. Mean concentrations found in the water of the different WWTP sections studied ± standard deviations (n = 3).

Table 2
Values of DWEL for different ages and PNEC of the studied pharmaceutical compounds (obtained from Sharma et al., 2019).

Pharmaceutical	DWEL (ng L^{-1})			PNEC (ng L^{-1})		
	1–2 years	16–21 years	>21 years	Algae	Daphnia	Fish
CBZ	4800	12800	10000	34000	14000	35000
DIC	947200	2523800	1964600	15000	22000	530000
IBU	1555100	4143500	3225500	4000	9100	170000
KET	70700	188300	146600	160000	250000	32000
NPX	650300	1732700	1348800	22000	15000	34000

in aerobic environments, while reductive transformation of this compound seems to be possible to some extent (König et al., 2016). The nonsteroidal anti-inflammatory DIC experienced an extraordinary variation during the treatment in the WWTP. The mean value detected in the influent was 69.5 ± 0.50 ng L^{-1}, while in the effluent the concentration was 307 ± 5.29 ng L^{-1}. The influent concentrations found in other studies were also lower than those obtained in the effluent (Kołecka et al., 2019). This is due to the fact that these compounds (CBZ and DIC) are very recalcitrant, and very hard to remove from wastewaters. For CBZ, Kruglova et al. (2014) reported that this behaviour could be explained by the presence of input conjugate compounds that during the treatment process are retransformed into the parental compounds. Also, the gradual release of CBZ adsorbed onto sludge during biological treatment can lead to an increased abundance of these compounds in WWTP effluents (Jelic et al., 2011). In the case of DIC, Kimura et al. (2005) demonstrated that its persistence was due to the presence of chlorine in its structure, which made it difficult to degrade during biological treatment.

The mean IBU concentration in the influent was 316 ± 9.52 ng L^{-1}, but along the depuration process, this pharmaceutical compound was gradually degraded, reaching a concentration in the effluent of 81.0 ± 8.00 ng L^{-1}. Afonso-Olivares et al. (2017) detected ibuprofen concentrations in the range of 16,100 ng L^{-1} to 21 ng L^{-1} in the influent and effluent of a WWTP in Spain. Nevertheless, in a similar study, Martínez-Alcalá et al. (2017) detected an influent concentration of 734 ng L^{-1} while that in the effluent was below the MDL.

The NPX concentration underwent a clear decrease during the WWTP processes, showing an initial concentration of 599 ± 36.3 ng L^{-1} that was reduced to 90.3 ± 10.5 ng L^{-1} in the effluent. The concentrations obtained were comparable to those found in other WWTPs of the Murcia Region, with concentrations of 444 and 11.5 ng L^{-1} in the influent and effluent, respectively (Martínez-Alcalá et al., 2017). While Afonso-Olivares et al. (2017) found influent and effluent concentrations of 1450 and 50 ng L^{-1}, respectively.

Regarding the concentrations found in the sludge (Fig. 4), only DIC, IBU and NPX were detected in the different parts of the WWTP, with the exception of the dehydrated sludge, where none of the compounds were detected. Diclofenac was not detected in reactor A (B.R.A), but it was present at 102 ± 13.4 ng g^{-1} in the first part of biological reactor B (B.R. B1) and at 130 ± 1.11 ng g^{-1} in the last zone of the reactor B (B.R.B2). In a study performed by Martínez-Alcalá et al. (2017), a diclofenac concentration of 33.6 ng g^{-1} was found in the aerobic phase of the biological reactor in a simple CAS WWTP.

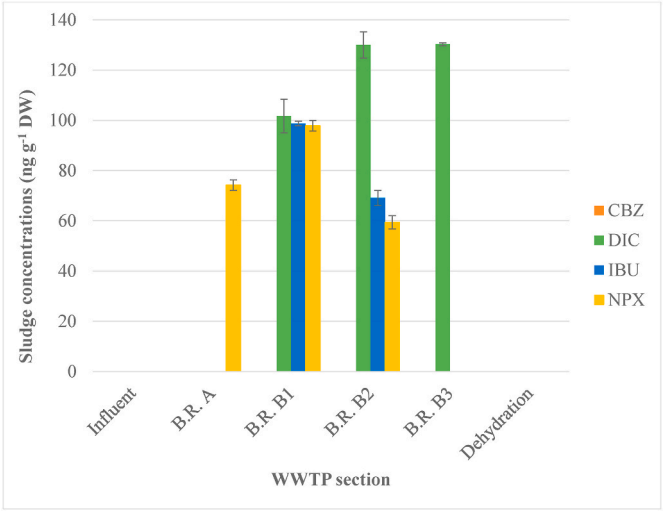

Fig. 4. Mean concentrations found in the sludge of the different WWTP sections studied ± standard deviations (n = 3).

Ibuprofen was detected in the first two zones of biological reactor B (1 and 2), with concentrations of 98.7 ± 1.76 ng g^{-1} and 69.1 ± 5.93 ng g^{-1}, respectively. Indicating that its concentration decreased during the purification process. The IBU concentrations found in the sludge were below those detected by Martín et al. (2012): 2206 ng g^{-1} in primary sludge and 1584 ng g^{-1} in secondary sludge. Nevertheless, other authors found concentrations similar to those described in the present experiment (Gago-Ferrero et al., 2015). The pharmaceutical NPX was detected in reactor A and in the first two zones of reactor B (1 and 2), with concentrations of 74.2 ± 4.09, 97.8 ± 4.14 and 59.4 ± 5.23 ng g^{-1}, respectively. These results are basically in concordance with other studies reported in the literature, with concentrations between 32.9 and 50.4 ng g^{-1} in the secondary sludge, not being detected NPX in the digested sludge (Martín et al., 2012).

3.2. Biological degradation rate constant (K_{biol}) and partitioning coefficient (K_d)

The intrinsic biodegradation constant (K_{biol}) provides a better understanding of the degradation of soluble compounds within a wastewater treatment process involving active sludge. These intrinsic degradation rates can be applied to any treatment. For our WWTP system, the values of the biological degradation constant were calculated for the biological reactor of stage B2 (Table 3).

According to Joss et al. (2006), drugs can be divided into three groups according to their degradation constants:

K_{biol} <0.1 (L g $MLSS^{-1}$ d^{-1}). These are persistent compounds whose biodegradation is low (<20%). This has been the case of CBZ, both here and in other studies [19, 20], showing its resistance to biological transformation.

0.1> K_{biol} <10 (L g $MLSS^{-1}$ d^{-1}). These compounds are moderately transformed in the biological reactor, with a removal percentage between 20 and 90%. This was the case here for DIC, IBU and NPX. Similar results (<0.5 L g $MLSS^{-1}$ d^{-1}) were obtained for DIC in other studies (Tauxe-Wuersch et al., 2005; Zwiener and Frimmel, 2003), while Suárez et al. (2010) obtained a value of 1.2 L g $MLSS^{-1}$ d^{-1}. In the case of NPX, the results are in good agreement with those obtained by Suárez et al. (2010), between 0.4 and 1.9 L g $MLSS^{-1}$ d^{-1}.

K_{biol}> 10 (L g $MLSS^{-1}$ d^{-1}). These compounds have a high removal percentage (>90%). Here, this value was not reached for any of the evaluated compounds, although it was exceeded for ibuprofen in the Joss et al. (2006) study, with values of 21–35 L g $MLSS^{-1}$ d^{-1} in a CAS WWTP. Nevertheless, Smook et al. (2008) obtained much lower K_{biol} values for ibuprofen (6.8 ± 3.3 and 8.4 ± 4.0 L g $MLSS^{-1}$ d^{-1} in a sequencing batch reactor and in a membrane bioreactor WWTPs, respectively).

Knowledge of the sorption of pharmaceutical compounds to the sewage sludge in a WWTP is a key factor in the understanding of their presence in the environment and in the risk evaluation. In the present case, the absorption coefficient in the first aerobic zone of the second biological reactor was measured. Unfortunately, some of the studied compounds had concentrations below the detection limits and therefore could not be determined. The highest K_d was obtained for DIC, while the lowest was for NPX. Hyland et al. (2012) obtained K_d values of 2.18 for diclofenac, 2.32 for IBU and 2.16 for NPX in activated sludge. These values are similar than those found in the present experiment, the

Table 3
Biological degradation constants (K_{biol}) and partition coefficients (log K_d) for the studied pharmaceutical compounds.

Pharmaceutical	K_{biol} (L gMLSS^{-1} d^{-1})	Log K_d (L kg^{-1})
CBZ	−1.18	–
DIC	0.30	3.09
IBU	0.57	2.82
NPX	0.53	2.67

differences in the WWTP and in the sludge, regarding to parameters like the total suspended solids, total organic carbon and chemical oxygen demand, could be responsible for these discrepancies. Moreover, there are other parameters such as the surface properties of the sludge and the mixed liquor pH – that are important in the control of the sorption of pharmaceutical compounds into sludge (Hörsing et al., 2011).

3.3. Removal of pharmaceutical compounds

For the calculation of the removal of pharmaceutical compounds from the water, the sorption in the sludge has not been taken into account and only the disappearance from the water of the parental compound under study has been used. Since the psychiatric drug (CBZ) was not detected in the influent of the WWTP, the calculation of its removal was not possible.

Among the non-steroidal anti-inflammatory drugs (DIC, IBU, KET and NPX), DIC exhibited a negative removal. According to Joss et al. (2006), 55–95% of the DIC in the influent can be removed, mainly by biological transformation (5–45%) plus a small amount of sorption onto the sludge (<5%). In a study of Peng et al. (2019), DIC could not be removed in any way and was persistent under aerobic conditions. The removal efficiencies of DIC in WWTPs vary greatly, from 0% to 80%, but are mainly in the range of 21–40% (Zhang et al., 2008). In the ibuprofen case, it was degraded effectively, with a removal value of 74%. For IBU, the greatest decrease occurred in the B.R.B 3 (76%). According to Suárez et al. (2010), between 60 and 65% of the IBU in the influent can be removed, mainly through biological transformation (35–40%) with no sorption onto the sludge. Peng et al. (2019) showed that IBU was removed mainly via nitrification and the chemical oxygen demand by a degradation process (heterotrophic biodegradation), and no adsorption occurred. In the current study, KET removal was not measured since the concentrations obtained were under the detection limits, while the NPX removal amounted to 85%. This result is in agreement with Tran et al. (2018), for whom the NPX removal from the influent was between 0 and 99%.

The tertiary treatment in WWTPs was observed in order to reduce the parental concentration of PPCPs regarding to WWTPs with only secondary treatment (Bulloch et al., 2015). In other study made in a WWTP of Murcia Region with a simple CAS (Martínez-Alcalá et al., 2017), was found that DIC removal was around 80%, while the removal for IBP and NPX were almost 100%. It reports that the double stage of the WWTP present no advantages above a simple CAS or than other parameters like, for example, a higher HRT (87 h) which could be more important for these compounds degradation. Furthermore, the complex relationship between the physico-chemical properties of the analysed compounds (such as those presented in Table 1) and the different pH values found in the mixed liquor of the WWTPs, give rise to a great variability of PPCPs removals (Tadkaew et al., 2010).

3.4. Human and ecological risk quotients

In order to estimate the risk quotients in the effluent in order to find out the worst possibility scenario of exposition through to this water, were used the pharmaceutical maximum concentration detected. To reduce uncertainty in the evaluation of human health risk, other researchers evaluated the risks for PPCPs in different age-exposures (Sharma et al., 2019; Yang et al., 2017b). In this study, the HRQs calculated ranged from 0.00003 to 0.02313 (Fig. 5 a). The pharmaceutical with higher HRQ was CBZ, followed by DIC. Although HRQs for babies were bigger than throughout adolescence and adulthood due to their lower body weight, all the HRQs values were below to 0.2 that is considered of no appreciable concern to human health (Yang et al., 2017b).

In the ERQs case, the values ranged from 0.022 to 0.0005 (Fig. 5 b). The pharmaceutical compound with higher ERQ was IBU, followed by DIC. From all the aquatic organism evaluated (algae, daphnia and fish),

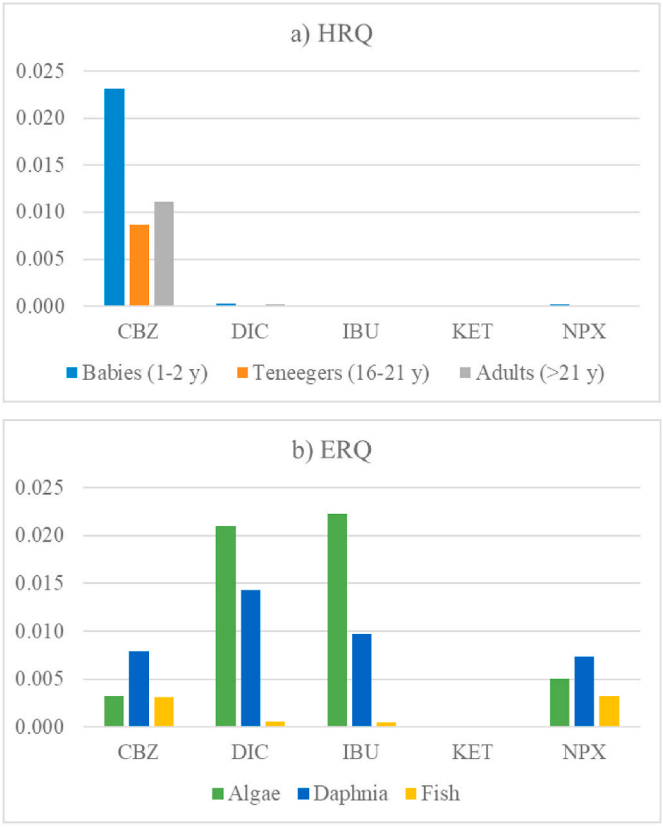

Fig. 5. Results of the a) Human risk quotient for babies (from 1 to 2 years old), teenager (from 16 to 21 years old) and adults (higher than 21 years old) and b) Ecological risk quotient for algae, daphnia and fish of the selected pharmaceutical compounds in the effluent of the WWTP.

the one that seems experience the greatest risk would be algae. In the study made by Yang et al. (2017b) the higher RQ was obtained for algae, that could be more sensible than the other species. Nevertheless, again the ERQ values are all under 0.1, so in this sense, no ecotoxicological risk would be produced (Hernando et al., 2006). These low values of RQs imply that the pharmaceutical concentration in the effluent WWTP does not represent an adverse risk to human and to ecosystem health when they are considered individually. When the pharmaceutical compounds are considered as a mixture, the result of add up all the RQ was lower than 1, so consequently these exposures are of low concern (Holmes et al., 2017).

Nevertheless, only were monitored a few pharmaceutical compounds comparing with whole of them. For that, the adverse consequences in the environment can be higher due to it can be found together with other substances, doing necessary more researches to confirm the risk absence.

4. Conclusions

The study evaluates the presence of five PPCPs belonging to different therapeutic classes - specifically, one psychiatric drug (CBZ) and four non-steroidal anti-inflammatory drugs (DIC, IBU, KET and NPX) - in water and sludge samples of a double stage WWTP from Murcia (Spain). The main aim was to compare the double stage CAS WWTP with the simple one. In the water samples, CBZ was masked in the influent and only appeared after the biodegradation process. The K_{biol} and K_d results indicate that this compound was neither removed by the microorganisms nor sorbed into the sludge, reflecting its recalcitrant behaviour in waters. The DIC was moderately biodegraded and was the compound that underwent the greatest sorption into the sludge (K_d) under these

experiment conditions, a negative removal was observed, probably due to its entry into the WWTP as a conjugated compound not detected by the analytical equipment. The other non-steroidal anti-inflammatory drugs (IBU and NPX) were moderately biodegraded during the WWTP processes, showing lower concentrations in the effluent than in the influent. The pharmaceutical removal was lower that the obtained in other experiment conducted in the same region in a simple CAS. In this sense, it can be observed that with this experimental conditions, the double stage system does not improve the removal of pharmaceutical compounds and that the simple CAS is more efficiently to eliminate them. It can be due to their higher HRT or the different physical-chemical parameters inside the reactor that could improve the pharmaceuticals degradation. Nevertheless, further studies should be done in order to confirm this.

The last aim was to evaluate if the effluent could represent any risk to the humans or the environment. In this case, the RQ values obtained do not appear to pose any threat. Regardless, more research about the mixture of different PPCPs and their transformation products or their long-term effects above human and ecosystems must be made in order to be completely sure.

Credit author statement

Isabel Martínez-Alcalá: Conceptualization, Investigation, Methodology, Data curation, Software, Data curation, Writing - original draft, Supervision. José Manuel Guillén-Navarro: Laboratory work, Writing - original draft. Agustin Lahora: Visualization, Investigation, Supervision, Writing- Reviewing and Editing

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2020.111565.

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