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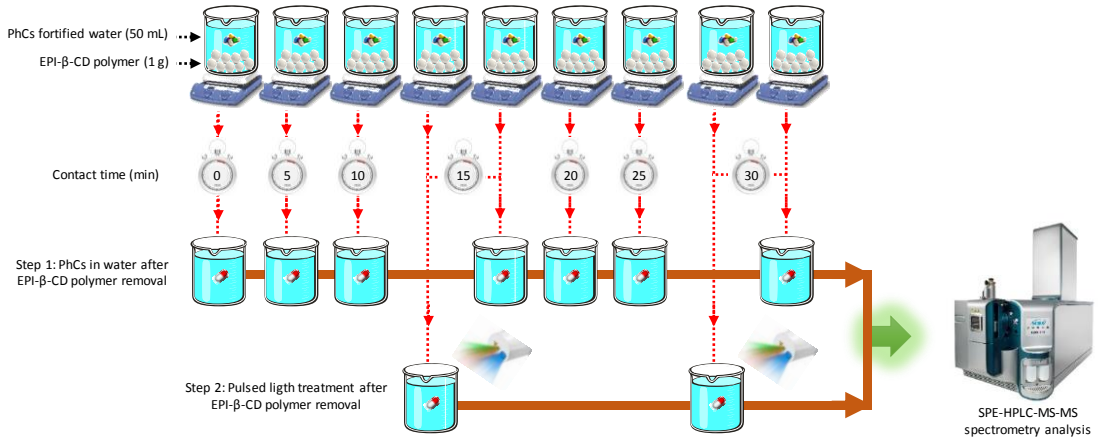
Graphical Abstract



Highlights

- Pharmaceutical compounds occurring in wastewater are an environmental concern.
- A novel process for removal emerging pollutants was developed.
- The process is a sequential treatment with cyclodextrins and pulsed light.
- The process removes pharmaceutical compounds from water by 91%.

Abstract

The presence of pharmaceutical compounds (PhCs) in the effluents of wastewater treatment plants (WWTPs) is an ecological concern. The issue could be alleviated by trapping those substances by cyclodextrin (CD) polymers or photolyzing them by pulsed light (PL). Consequently, a sequential CD polymer/PL system was tested for the removal of PhCs. Firstly, a survey detected the presence of recurrent PhCs in the effluents of local WWTPs. Then, pure water was spiked with 21 PhCs, 100 µg/L each one. The three-dimensional network provides amphiphilic features to the CD polymer that reduced the pollutant concentration by 77%. Sorption involves a plead of physical and chemical mechanisms hindering the establishment of a general removal model for all compounds. The performed simulations hint that the retention capacity mainly correlates with the computed binding energies, so that theoretical models are revealed as valuable tools for further improvements. The complementary action of PL rose the elimination to 91 %. The polymer can be reused at least 10 times

for ibuprofen (model compound) removal, and was able to eliminate the ecotoxicity of an ibuprofen solution. Therefore, this novel sequential CD polymer/PL process seems to be an efficient alternative to eliminate PhCs from wastewater.

Keywords: emerging pollutants, cyclodextrin, pulsed light, wastewater treatment, environmental contamination.

1. Introduction

The evaluation of the impact of chemical pollution during many decades has been mostly focused on pollutants with a risk to human health due to their toxicity, carcinogenic and mutagenic effects, and their persistence in the environment (Daughton and Ternes, 1999). The development of more powerful analytical techniques in the last years has allowed the detection of numerous chemical compounds present in water at very low concentrations, the so-called emerging pollutants (EPs), leading to concerns on the impact these compounds may have on human health and aquatic life (EPA, 2010). Its emerging terming do not refer to new occurrence but to the recent awareness of their presence and awakened concern among the scientific community. EPs include pesticides, flame retardants and pharmaceutical compounds (PhACs). Many PhACs enter municipal wastewater through the disposal of human and animal wastes and unused pharmaceuticals, and arrive to wastewater treatment plants (WWTPs). These plants are not designed to specifically remove EPs from wastewater. Consequently, although some level of removal does occur, water contaminated with these compounds is released to the environment (EPA, 2010; Couto et al., 2019). Effluents from pharmaceutical manufacturing facilities are also an important source of PhCs released to the environment; a national survey carried out in the USA, detected concentrations of these kind of compounds in their influenced effluents more than 3,000 times higher than in control sites (Scott et al., 2018). EPs may be candidates for future regulation, depending on research on their potential health effects and monitoring data regarding their occurrence (Barceló, 2005). Due to their continuous introduction into the environment, EPs

can be considered as “pseudo-persistent” pollutants, which may be able to cause the same exposure potential as regulated persistent pollutants, since their high transformation and removal rates can be compensated by their continuous input into the environment (Gros et al., 2006). Target 6.3 of the United Nations Sustainable Goals calls for actions to “improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals” (UN, 2015). Likewise, goals 3 and 12, which are focused on good health and well-being and responsible consumption and production respectively, are also related to the urgent need to reduce the release of harmful compounds to the environment (UN, 2015).

Some of the strategic approaches outlined by the European Commission to reduce the threat posed by pharmaceuticals to the environment consist of investing in technologies to improve the removal of PhCs, and investigate the feasibility of upgrading WWTPs (EU, 2019). Therefore, there is a need to search for efficient methods to eliminate EPs from wastewaters. While this is a very active research field, no consensus has been reached about the most appropriate technologies, and site-specific limitations may lead to different conclusions (Rizzo et al., 2019). One method that may be used to remove EPs from wastewaters is separation by using cross-linked cyclodextrins (CDs), which has been studied to remove drugs from the environment since the 90s (Morin-Crini et al., 2018). CDs are natural molecules derived from starch that allow the formation of inclusion complexes with several organic compounds into their hydrophobic cavity, either in solution medium or in solid phase, a property that has been recently exploited to remove contaminants from wastewater (Semeraro et al., 2015). They can be cross-linked by polymerizing agents such as epichlorohydrin to form an insoluble network of larger size, and with different properties than those of the initial CDs monomer, easily removable from wastewater after the pollutants adsorption (Gidwani and Vyas, 2014) and reusable, since once saturated, the polymer can be regenerated by a chaotropic agent, allowing their use several times. Indeed, the three-dimensional network formed, confers to the polymer amphiphilic features with both, hydrophilic properties due to the occurrence of glucose units (CDs), mainly hydroxyl groups, and hydrophobic properties, mostly due to the methyl groups and ether bonds of the cross-linking agent, and CD-glyceryl bonds.

This is advantageous in the removal of trace levels of pollutants in complex solutions, versus conventional sorbents like active carbon or ion exchange resins (Romo et. al, 2008). Thus, its good performance has been exploited for environmental applications, especially the elimination of EPs in aqueous media, enabling polymer to trap pollutants through additional interactions (external to the inclusion sites), that supplement the sorption capacity considering inclusion complexes alone. Owing to this additional binding, it has been demonstrated that the stability constants of these pollutant complexes are often greater than those of native CD-pollutant interactions, justifying the whole range of sorption results described for polymer network (Morin-Crini and Crini, 2013).

Although the manufacturing process has to be done with great care given the toxicity (by contact and inhalation) of the bifunctional coupling agent, epichlorohydrin has advantages over other crosslinkers such as diisocyanate (high reactivity, yield, mobility of the polymer network and marked hydrophobic properties) (Wilson et. al, 2010). In addition, the obtained CDs polymers result completely non-toxic for human health (Mura et al., 2002), and based on the literature (Verstichel et al. 2004), should be speculated that cyclodextrin-epichlorohydrin polymer could be slowly biodegraded reducing the environmental risks.

Photolysis is another method that has been evaluated for the elimination of water pollutants. It is generally carried out by low-pressure mercury lamps. The photolytic degradation of EPs can also be accomplished by pulsed light (PL) technology. PL technology consists in the application of short pulses of high-energy wide-spectrum light (Pellicer et al., 2018). It is a photonic method initially developed for use in the food industry to inactivate microorganisms. However, in the last decades, the field of application of PL technology has been diversified to different uses, including the degradation of water contaminants. PL is able to degrade pesticides (Baranda et al., 2014) and when combined with hydrogen peroxide can also degrade textile dyes (Martínez-López et al., 2019). EPs are present in wastewater not as single compounds, but as a mixture of chemical compounds with different properties, including different absorption spectra. The emission spectrum of PL lamps can be especially suitable for the elimination of mixtures of emerging contaminants in wastewaters when compared to

conventional light sources. The direct photolytic degradation of chemicals is only possible when the emission spectrum of a given light source overlaps the absorption spectrum of the compound. Classical light sources are either low-pressure or medium-pressure mercury lamps. The first kind emits monochromatic light at 253.7 nm, which is not absorbed by all emerging contaminants; while the latter emits several lines from 205 to above 500 nm (Pereira et al., 2007). In contrast, the emission of PL lamps is a continuous that overlaps any absorption spectrum and includes an important amount of UV light (Gómez-López et al., 2007). Furthermore, PL is more environmentally friendly than other light sources because lamps are filled with xenon, which is less harmful to the environment than mercury (Gómez-López et al., 2007). This fact is especially relevant taken into account that more than 100 countries have signed the Minamata Convention on Mercury (UNEP, 2017), aiming to reduce mercury use worldwide. To the best of our knowledge, pulsed light has never been tested for the degradation of PhCs.

Currently, there is no single method able to remove the whole range of emerging contaminants present at very low concentrations from effluents that are heterogeneous and variable in nature. As have been reviewed in the literature (Morin-Crini et al., 2018; Sikder et al., 2019), modified CDs, especially with epichlorohydrin, can attain elevated sorption in wastewater treatment toward a wide range of pollutants, including pharmaceuticals, showing that it is important not only to take into account the characteristics of the polymeric material (CD content, degree of cross-linking, swelling ratio and pore size), but also the interactions between the three components of the sorption system (i.e. the polymer, the pollutant and the water to be decontaminated) to achieve good results. However, between polymeric sorbent and the pollutant to be eliminated, different physical and chemical mechanisms are involved, mainly a chemisorption mechanism by inclusion into CDs cavity, to which we must add the possibility to sequester pollutants through effects of cooperation between CDs and/or via additional interactions in the mesh with diffusion into the polymer network (García-Zubiri et. al, 2009). In addition, the structure and the polarity of the pollutants studied as well as the experimental conditions (dosage of material, pollutant concentration, pH, ionic strength, etc.) of the batch used can also contribute to complicating the interpretations, difficulty that may be increased if

real wastewater containing multiple contaminants will be studied. In fact, a recent study carried out at small scale laboratory reported that the removal of nine emerging pollutants by a cyclodextrin polymer ranged from 13 to 99 % (Nagy et al., 2014). Even if the CD-epichlorohydrin polymer removed efficiently most of the micro-pollutants, especially the bisphenol-A (94%) and hormones (87–99%), results were not allowing establish a general removal model for all compounds.

Therefore, a complementary method is needed to eliminate the residual amount of compounds remaining in water after going through the polymer. In this sense, PL is a green technology that has been proven effective in the degradation of a wide range of organic compounds. The efficacy of PL is seriously impaired by water turbidity, which absorbs light and shields the pollutants from light absorption, therefore, the previous use of a CD-polymer in a real-life scenario would be useful, not only to retain PhC, but also organic matter that would otherwise difficult the photolytic process. Furthermore, a reduction of PhC concentrations by CD-polymers prior to PL treatment would leave lower amounts of contaminants to be photolyzed, saving time and energy consumption. In this sense, coupling sorption on CD polymer materials followed by PL treatment could be efficient for the treatment of effluents urban wastewaters from a chemical and an environmental point of view. As consequence, the goal of this research was to evaluate the efficacy of a sequential CD polymer/PL process to abate the concentration of PhCs in water

2. Experimental work

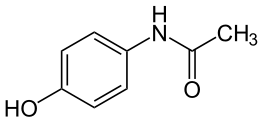
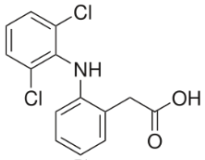
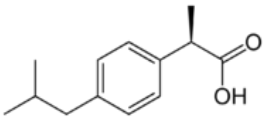
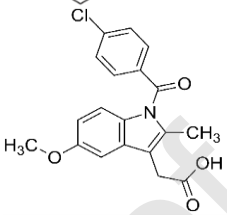
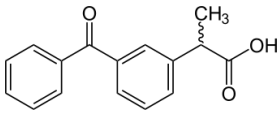
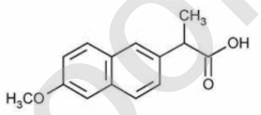
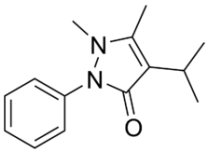
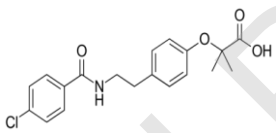
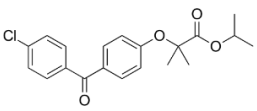
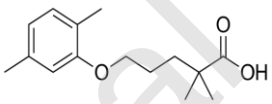
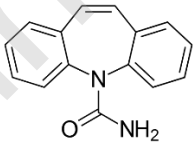
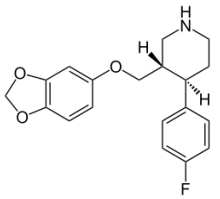
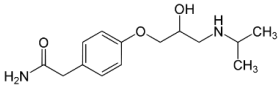
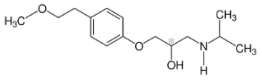
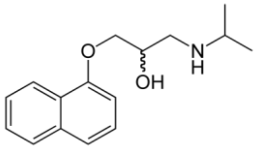
2.1. Materials

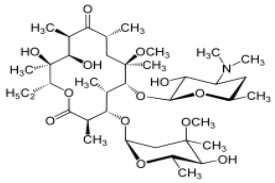
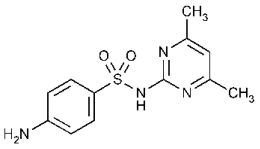
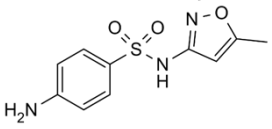
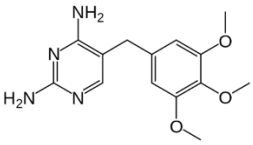
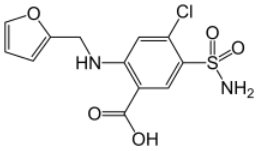
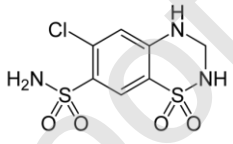
A commercial β-cyclodextrin bead polymer (CYL-1502, grain size: 0.1 – 0.3mm, swelling volume: 4 ± 1 mL/g, β-cyclodextrin content 60%), using epichlorohydrin as cross linker agent (EPI-β-CD polymer), was purchased from Cyclolab Ltd. (Budapest, Hungary).

A stock solution of 21 PhCs (table 1) was provided by Instituto de Diagnóstico Ambiental y Estudios del Agua (CSIC), Barcelona, Spain. HPLC-grade water was fortified with the stock solution to a final concentration of 100 µg/L of each compound. The standards were purchased in Sigma Aldrich (Barcelona, Spain).

Ibuprofen used in the reusability test was purchased from Santa Cruz Biotechnologies (Dallas, USA).

Table 1. Pharmaceutical compounds used to spike water.

Name	Structure	Name	Structure
Analgesics and anti-inflammatories			
Acetaminophen		Diclofenac	
Ibuprofen		Indomethacin	
Ketoprofen		Naproxen	
Propyphenazone			
Lipid regulators			
Bezafibrate		Fenofibrate	
Gemfibrozil			
Psychiatric drugs			
Carbamazepine		Paroxetine	
β-blockers			
Atenolol		Metoprolol	
Propanolol			

Antibiotics			
Clarithromycin		Sulfamethazine	
Sulfametoxazole		Trimethoprim	
Diuretics			
Furosemide		Hydrochlorothiazide	

2.2. Determination of the presence of pharmaceutical compounds in treated wastewater effluents

One-liter samples from the WWTPs were collected in soda-lime glass bottles (Labbox, Barcelona, Spain), at the exit pipes and transported at 4 ºC to the laboratory within one day. Samples from WWTPs coded 1, 2 and 3 were taken after secondary treatment and from WWTPs coded 4 after a tertiary treatment with UV light. Samples 5a and 5b were taken from the same plant, 5a after the secondary treatment and 5b after a tertiary treatment with chlorine. Concentrations of the PhCs atenolol, carbamazepine, ciprofloxacin, diclofenac, ketoprofen, norfloxacin, sulfamethoxazole, sulfathiazole and trimethoprim were determined by a certified external laboratory by on-line SPE-HPLC-MS-MS spectrometry.

2.3. Sequential cyclodextrin polymer/pulsed light treatments

Spiked water was used to test the adsorption capacity of the cyclodextrin polymer. In brief, one gram of EPI-β-CD polymer was mixed with 50 mL of fortified water. This mixture was stirred at 900 rpm for different contact times: 0 (as control, no CDs polymer), 5, 10, 15, 20, 25 or 30 min, and then centrifuged at 18,000 g for 10 min. Supernatants were used for analysis. Additionally, supernatants corresponding to 15 and 30 minutes of the abovementioned

procedure were collected and subjected to pulsed light treatment as indicated in fig. 1. Tests were carried out by triplicate. For the photolytic experiments, 25 mL of water sample was placed in a Petri dish without cover and treated with PL in a XeMaticA-Basic-1L unit (Steribeam, Kehl, Germany). This system can be operated at different voltages. In this case, a discharge voltage of 2.5 kV was used, which generates a light with an energy of 500 J/pulse (2.5 MW) and 21% of UV component. The flash has a pulse width of 200 µs and a characteristic polychromatic emission spectrum reported before (Cudemus et al., 2013). The fluence incident on sample surface was 2.14 J/cm^2 per pulse. Incident fluence was determined by photodiode signal analysis using a PC-Lab 2000 LT PC oscilloscope (Velleman Instruments, Belgium) and manufacturer performance charts. Different fluences were provided to samples by applying multiple pulses. Samples were treated with 45 light pulses, in triplicate.

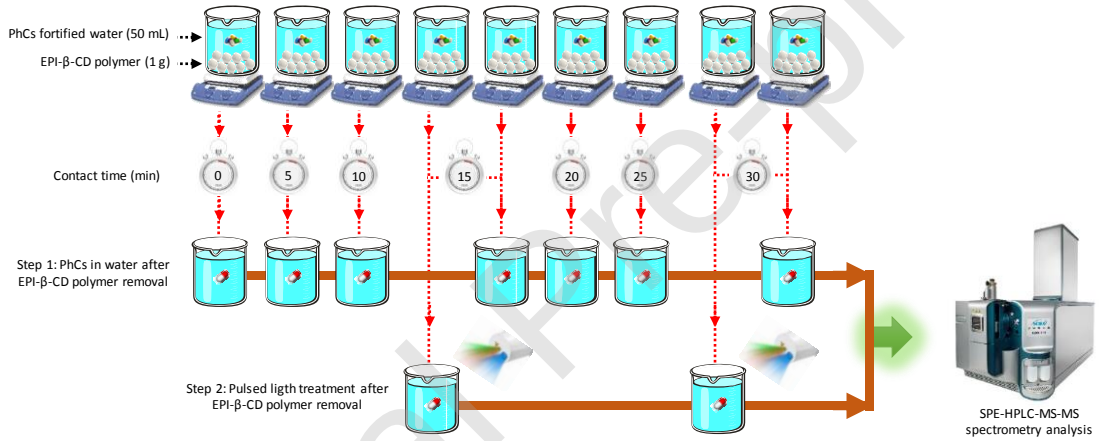


Figure 1. Flowchart of the experimental set-up.

PhCs concentrations in tests samples with pure water were determined by liquid chromatography MS/MS spectrometry. To this, direct analysis of the samples was performed using a X500R QTOF system (Sciex, Redwood City, CA, USA), equipped with a TurboV Ion source, and operated in electrospray ionization (ESI) in positive mode controlled by SCIEX OS software. UHPLC separation was performed using 100 mm × 2 mm Purospher STAR RP-18 end-capped column (2-µm particle size) at 40 ºC (Merck, Darmstadt, Germany). The injection volume was 10 µL.

In positive ion mode, a standard reverse phase gradient was used with an aqueous phase with 0.1% formic acid and 5mM ammonium acetate and

acetonitrile, at a flow rate of 0.4 mL min^{-1} with the initial conditions (5% acetonitrile) were maintained for 0.5 min before the organic solvent increased from 5 to 98 % in 15.5 min. 98 % organic conditions were held for 3 min before returning to the initial conditions in 6 s, which were maintained for 5.0 min to allow column re-equilibration before the next injection. This gradient provided a chromatographic analysis time of 24 min.

For negative ion mode, the mobile phases were (A) water with 5mM ammonium acetate and (B) acetonitrile at a flow rate of 0.4 mL min^{-1}. Initial conditions (5% acetonitrile) were maintained for 0.5 min before the organic solvent increased from 5 to 73% in 11.5 min and then to 100% in the following 0.5 min. Pure organic conditions were held for 40s before returning to the initial conditions, which were maintained for 1.8 min to allow column re-equilibration before the next injection. This gradient provided a chromatographic analysis time of 15 min.

MS data were collected in multiple reactions monitoring high resolution (MRM^{HR}), using optimized source conditions. The MS mass range was m/z 100-800 and the MS/MS was acquired with a mass range of m/z 50-700 the accumulation time of 25 m*sec*. Transitions from the precursor ion to two of its main fragment ions were recorded for each target compound. One MRM transition was selected for each surrogate standard. Selected MRM transitions for each analyte are summarized in Table S1 for the negative ion mode and in Table S2 for the positive ion mode.

2.4. Reusability of the cyclodextrin polymer

Ibuprofen, one of the components of the mixture of substances used in the previous experiments, was selected to assess the reusability of the polymer. A solution of 2 mg/L of ibuprofen in water was prepared. 50 mL of this solution was mixed with 1 g of polymer, stirred during 10 min at 700 rpm and centrifuged 5 min at 2,700 g (Eppendorf 5810, Eppendorf AG, Germany). Then, a sample of the supernatant was withdrawn and the remaining concentration of ibuprofen was determined by HPLC (Agilent 1200, Agilent, USA) according to Jun et al. (2015). The supernatant was discarded and another 50 mL of fresh ibuprofen solution was mixed with the polymer, stirred and centrifuged; the procedure was repeated 10 times. Then, the polymer was dried at 45 ºC overnight, and the contaminant

desorbed by using acetate buffer 220 mM, pH 4 and stirring at 700 rpm for 15 min. This mixture was centrifuged 5 min at 2,700 g and this procedure was repeated once more in order to regenerate the polymer. The polymer was once more dried at 45 ºC overnight and then used for a new cycle up to 10 cycles.

2.5. Acute toxicity test

The effect of the CD polymer/pulsed light system on the ecotoxicity was assessed using 2 mg/L ibuprofen solution as a model compound. A volume of 12 mL of samples were used for the acute toxicity test with the crustacean *Thamnocephalus platyurus*. This test was carried out according to ISO 14380 (2011) using larvae hatched from cysts (Thamnotoxkit F, MicroBioTest Inc., Nazareth, Belgium) during 20–22 h before the assay in a standard freshwater (dilution 1:8 with deionized water) at 25 °C under continuous illumination (3000–4000 lux). Tested samples were: 2 mg/L ibuprofen dissolved in water before and after CD polymer and CD polymer/PL treatment and 2 mg/L ibuprofen dissolved in acetate buffer and treated with PL. Simultaneously, three controls were run, a solution of 10 mg/L of $K_2Cr_2O_7$ (positive control), distilled water (negative control) and acetate buffer. The latter control was necessary to evaluate its ecotoxicity since the ibuprofen eluted from the polymer and then PL treated were dissolved in this solvent, which is used to regenerate the polymer. The treatment consisting in ibuprofen in acetate buffer and treated with PL was necessary since once PhCs are eluted from the polymer must also be degraded before releasing the elute to the environment. Tests were performed in 24-well plates with 10 crustaceans/well (1.0 mL of test solution), in three replicates. Serial dilutions from 0 to 100 % of the concentration from column 1 to column 6 were made within each Petri dish.

The results are presented in toxicity units (TU):

$$TU = [1/LC50] \times 100$$

where LC50 means 50% of test reaction-survival.

Liquid toxicity assessment has been based on a toxicity scale of environmental samples (Kalinowski and Zaleska-Radziwill, 2011¸ Persoone et al., 2003):

$TU < 1$: non toxic

$1 \leq TU < 10$: toxic

10 ≤ TU < 100 : acute toxic

100 ≤ TU: very toxic

2.6 Computational methods

Theoretical simulations have been performed to assess the encapsulation phenomena. Our computational protocol includes an initial optimization of both pharmaceutical compounds and the β-CD moiety. That early stage is conducted within the density functional theory (DFT) at the M06-2X/6-311G(d,p) level (Zhao et al., 2008). The resulting model systems are subsequently implemented in a docking simulation with Autodock Vina code (Trott et al., 2010), which have been previously used for predicting the encapsulation ability of CDs (Cerón-Carrasco et al., 2016). In that approach, β-CD entity is frozen in the space while drugs are treated as flexible systems around all rotatable bonds. Docking simulations provide a reliable description of the encapsulation process, with a focus on the possible binding modes (poses) of drugs inside the core region of CDs (Wang et al., 2019). However, energies need to be further improved with higher levels of theory if macroscopic evidences are looked for (Greenidge et al., 2014). Consequently, our predictions are refined with Prime (Jacobson et al., 2002; 2004) as implemented in the Schrödinger suite (Schrödinger, 2019). That final theoretical step provides more accurate binding energies derived from the difference between the energy of the pharmaceutical compounds as it is in the complex with β-CD and the energy of the free drugs, which are eventually used for delineating the measured extraction yield.

3. Results and discussion

3.1. Detection of pharmaceutical compounds in WWTPs

The aim of this research was to test the efficacy of a sequential cyclodextrin polymer/pulsed light process to eliminate EPs that can be of general use. However, the goal of the project that supports it is to implement this solution, which will be carried out in our province as starting point. Consequently, a survey in the effluents of different WWTPs of Región de Murcia (Spain) was conducted in order to detect the potential presence of PhCs in their treated effluent. A wide variety of PhCs were detected in the five WWTPs evaluated over a period of two

years (table 2, details can be seen in table S3 of supplementary materials). The type of detected compounds and their concentrations were variable among WWTPs and sampling days, but the presence of compounds belonging to different pharmaceutical families was conclusive. Compounds such as the anti-inflammatory drug ketoprofen were detected several times at concentrations higher than 3 µg/L. Others, such as the psychiatric drug carbamazepine and the anti-inflammatory drug diclofenac were detected every sampling day in each WWTP. The presence of some of these compounds, namely, carbamazepine, diclofenac and ketoprofen, has been reported in 2016 in the Roldán's WWTP, which is also located in the Región de Murcia (Spain); where ibuprofen and naproxen were also detected (Martínez-Alcalá et al., 2017). Previously, carbamazepine, diclofenac, ketoprofen and naproxen had been detected in a survey conducted over 12 WWTPs, which together purify 70 % of the wastewater of the Región de Murcia (Fernández-López et al., 2017).

Table 2. Mean concentration (µg/L) of pharmaceutical compounds detected in effluents of WWTPs from Región de Murcia (Spain) from February 2017 to April 2018 during eight sampling days. Values are means (range within parenthesis).

	WWTPs code*					
Compound	1	2	3	4	5a	5b
Atenolol	0.39 (0.17-0.73)	0.14 (<0.01-0.22)	0.19 (<0.01-0.33)	0.15 (<0.01-0.26)	0.17 (<0.01-0.31)	0.23 (<0.01-0.55)
Carbamazepine	0.22 (0.12-0.48)	0.18 (0.07-0.29)	0.75 (0.22-1.93)	0.24 (0.13-0.53)	0.17 (0.17-0.30)	0.12 (0.05-0.24)
Ciprofloxacin	0.76 (0.36-2.73)	0.41 (0.13-1.82)	0.13 (<0.03-0.37)	0.11 (<0.03-0.41)	0.54 (0.13-1.78)	0.17 (<0.03-0.36)
Diclofenac	1.58 (0.53-5.73)	3.14 (0.06-21.9)	0.81 (<0.01-3.2)	0.49 (0.18-1.80)	0.92 (0.26-2.5)	0.94 (0.18-2.69)
Ketoprofen	2.28 (0.38-3.96)	0.77 (<0.03-2.14)	0.11 (<0.03-0.52)	0.08 (<0.03-0.25)	0.54 (<0.03-2.15)	2.45 (0.58-4.73)
Norfloxacin	0.19 (<0.03-0.39)	0.16 (<0.03-0.43)	0.12 (<0.03-0.34)	0.06 (<0.03-0.28)	0.31 (0.13-0.78)	0.31 (<0.03-0.52)
Sulfamethoxazole	0.24 (<0.01-0.60)	0.05 (<0.01-0.13)	1.18 (0.18-6.5)	0.12 (<0.01-0.28)	0.12 (<0.01-0.34)	0.21 (<0.01-0.48)
Sulfathiazole	<0.01	0.02 (<0.01-0.05)	0.07 (<0.01-0.15)	<0.01	<0.01	<0.01
Trimethoprim	0.11 (<0.01-0.24)	0.01 (<0.01-0.03)	0.06 (<0.01-0.21)	0.03 (<0.01-0.07)	0.05 (<0.01-0.12)	0.09 (0.05-0.17)

* WWTPs codes. Samples 1-3 were taken after secondary treatment and sample 4 after a tertiary treatment with UV light. Samples 5a and 5b were taken from the same plant, 5a after the secondary treatment and 5b after a tertiary treatment with chlorine.

3.2. Cyclodextrin treatment

Among different sorption materials proposed for wastewater treatment with emerging contaminants, CDs cross-linked with epichlorohydrin are by far the most widely studied sorbents. As it has been described in the literature (Liu et al., 2001), the degree of cross-linking is pivotal on the physicochemical properties of the polymeric materials, and therefore, in its absorption efficacy (Romo et al, 2008). Thus, employing sorbents with stated cross-linking density and uniform characteristics is desired. In this sense, an epichlorohydrin cross-linked β-CD (EPI-β-CD) bead polymer synthetized by Cyclolab Ltd. (Budapest, Hungary), was used in this research because is the only commercial available material for which its reproducibility is confirmed (Morin-Crini et al., 2018).

The treatment with this polymer was able to decrease the concentration of PhCs in water by 77 %. The analysis of results evidence that the removal of contaminants by the EPI-β-CD polymer is very fast (figs. 2-4). After five minutes' contact time, the concentration of contaminants was abated by 71 %.

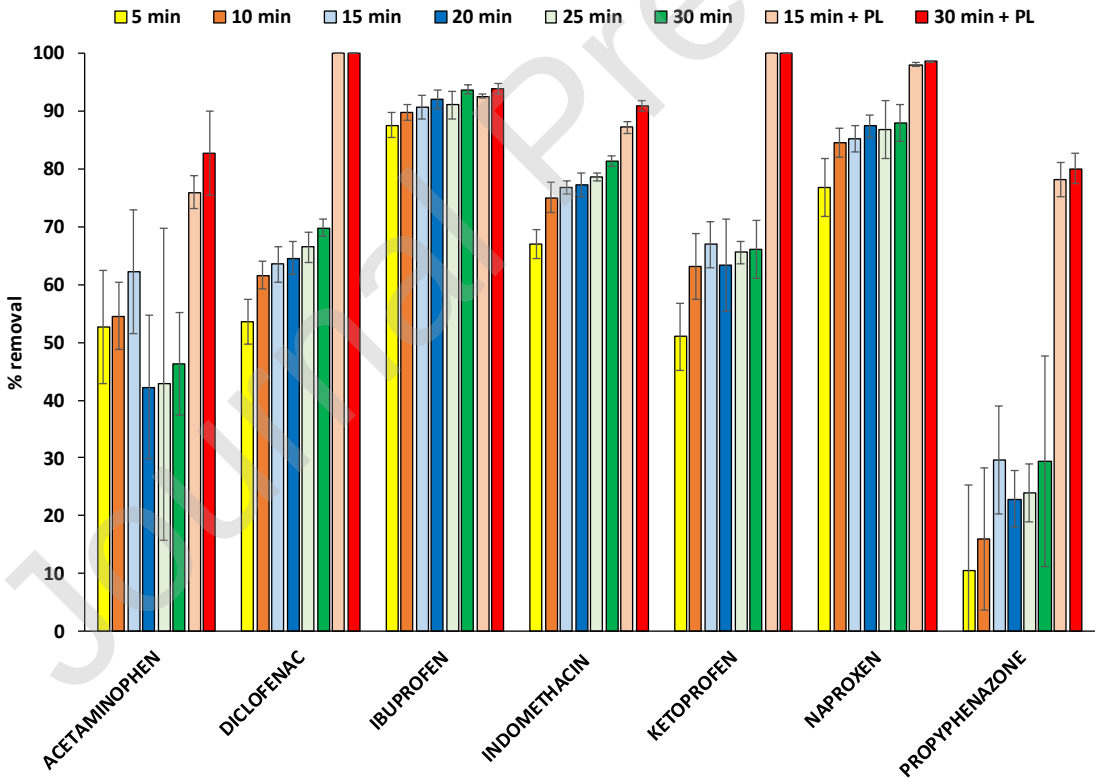


Figure 2. Removal of anti-inflammatory drugs from water by a cyclodextrin/pulsed light treatment.

Increasing the contact time to 15 min rises the abatement efficiency to 76 %, but increasing it to 30 min yields only an additional 1 %. However, while some compounds such as metoprolol, paroxetine and propranolol (fig. 4) were almost completely eliminated (99 %) after only 5 min, the use of longer contact times enhanced the elimination of some other compounds.

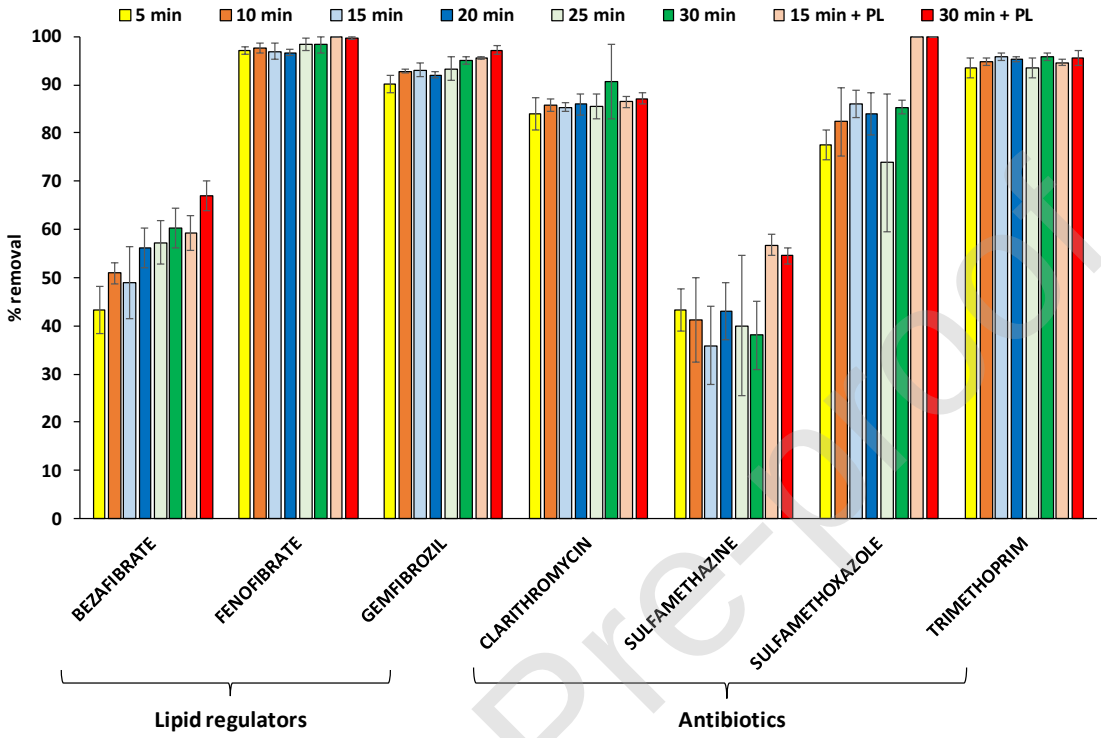


Figure 3. Removal of lipid regulators and antibiotics from water by a cyclodextrin/pulsed light treatment.

For example, propyphenazone (fig. 2) was the poorest adsorbed compound, it was eliminated by only 11 % after 5 minutes, but prolonging the contact time to 30 min allowed 30 % of elimination. The order of decreasing removal after 30 min was β-blockers > psychiatric drugs > lipid regulators > antibiotics > anti-inflammatories > diuretics, with respective removal efficiencies of 98, 89, 85, 78, 68 and 55 %.

Comparison of these results with the literature data is difficult because besides differences in experimental set-ups, there is a competence for the EPI-β-CD polymer by the different compounds dissolved in water. Therefore, removal rates will be affected by the type of compound spiked to water and the relative amount of them on molar basis as well as their size, stereochemistry and polarity.

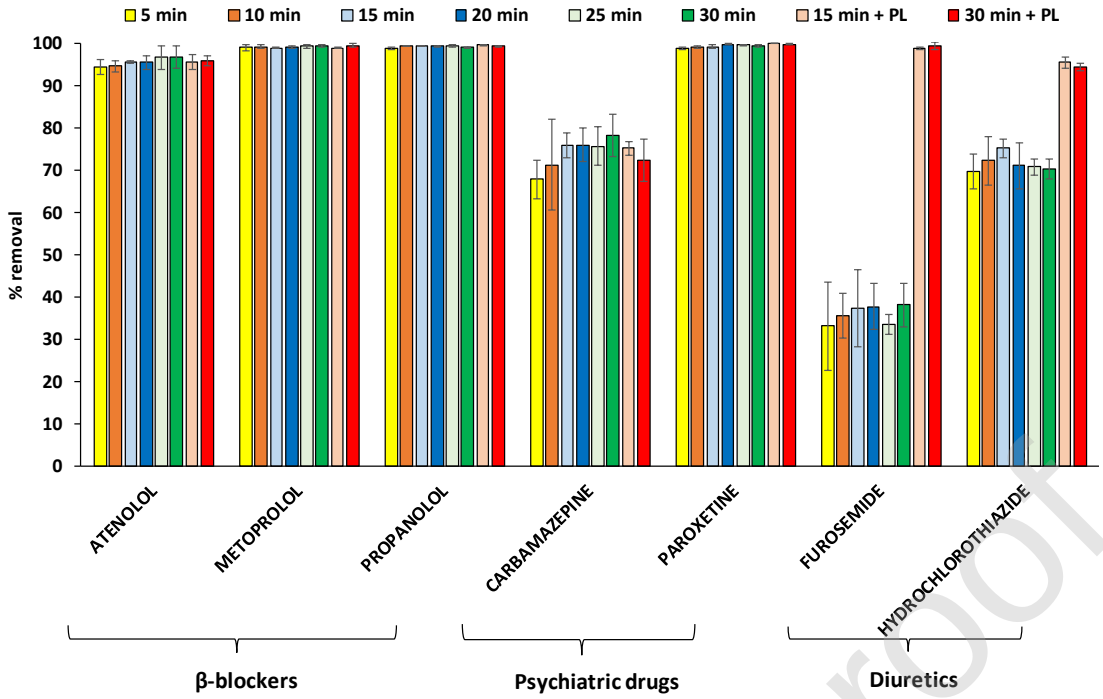


Figure 4. Removal of psychiatric drugs, β-blockers and diuretics from water by a cyclodextrin/pulsed light treatment.

For example, Nagy et al. (2014) used the same commercial cross-linked CD as used here, and spiked water with nine compounds including four PhCs at different concentrations. They reported removals of 13, 15, 35 and 67 % for ketoprofen, diclofenac, ibuprofen and naproxen respectively, while we have found removal levels of 66, 70, 94 and 88 % respectively (fig. 2).

All accumulated data hint that several effects might be simultaneously affecting those absorption yields, so that the prediction of a relative order of sorption as function of a parameter is not a trivial task. As recently described (Morin-Crini et al., 2018), amphiphilic cross-linked EPI-β-CD polymer possesses both hydrophobic and hydrophilic cavities of chaotic nature and hence random distribution of shapes and sizes that must be taken into account to explain the results obtained. Thus, hydrophilic properties of polymer allow it to interact with water, not only leading to better hydration (with the possibility to form hydrogen bonds) but also better swelling of the network (thus a greater potential for diffusion). In addition, the hydrophobic cavity of the CDs and cage structures

formed by the cross-linker rich in ethylene oxide groups, attracts hydrophobic drugs.

Overall data reveal that nine compounds (43% of the total), namely atenolol; clarithromycin, fenofibrate, gemfibrozil, ibuprofen, metoprolol, paroxetine, propranolol and trimethoprim (figs. 2-4) reached a very high adsorption (removal > 90 %) from the water after 30 min. Although hydrophobic interactions will be mainly implied in mechanisms of sorption of hydrophobic drugs (see supplementary material, Table S4), hydrophilic properties of polymer will play crucial role to enhance sorption of atenolol, metoprolol, paroxetine, propranolol and trimethoprim with lower hydrophobicity coefficients. In addition, formation of association complexes due to the CDs or polymer network should be considered for bulky clarithromycin. In addition, good sorption results (> 75-90 %) were obtained for hydrophobic drugs carbamazepine, indomethacin and naproxen, as well as for more hydrophilic sulfametoxazole, justifying sorption values by pKa (see supplementary material, Table S4) by hydrophilic interactions. At neutral pH sulfametoxazole is in ionized form accentuating, delocalization of the resonance charge, their electron density and polarizability, increasing the ability to interact via hydrogen bonding with polymer network (Yilmaz et al., 2010). A similar behavior highlighting hydrophilic interactions with EPI-β-CD polymer, could justify the high retention of hydrochlorothiazide, whereas the coefficient of hydrophobicity of bezafibrate, diclofenac and ketoprofen justify more relevance of hydrophobic interactions, achieving sorption results in the range (60-75 %). The poorest sorption results (< 50 %) were obtained for acetaminophen, furosemide, propyphenazone, and sulfamethazine, that could be conditioned by the reduced size of acetaminophen that hampers adequate polymer interaction, presence of ionized forms of furosemide and propyphenazone, unable to proper delocalization of the resonance charge hindering adequate interactions with polymer network and presence of methyl groups reducing its tendency towards to interact with polymer network via hydrogen bonding. An attempt to correlate the water solubility of the EPs with their experimental degree of retention by the EPI-β-CD polymer failed (R^2=0.30), revealing the complexity to elucidate sorption mechanism involved between a solution of pollutants with different physical-chemical properties and an amphiphilic polymer network, when no apparent

consistent trend was obtained, and could be strongly influenced by stereochemistry of analyte.

Aiming to further clarify the experimentally observed dissimilarities, we decided to mimic the encapsulation of the pharmaceutical compounds into β-CD by using computational simulations considering that chemisorption by inclusion into hydrophobic β-CDs cavity, is a key step upon interaction between polymer and pollutants. Therefore, one expects that the most hydrophobic molecules present a greater affinity to cyclodextrins (Morin-Crini et al., 2018). Consequently, we focus our computational efforts in mimicking the encapsulation phenomena by combining three levels of theory (i.e. DFT, docking and Prime).

Our calculations demonstrate that all drugs fit into the central core of the β-CD (see fig. 5). However, the conducted simulations lead to significant differences depending on each specific case (all computed binding energies are listed in Table S4). As in the case of water solubility, it is not observed a direct/simple linear correlation between binding energy and degree of retention, which points a competition among simultaneous effects.

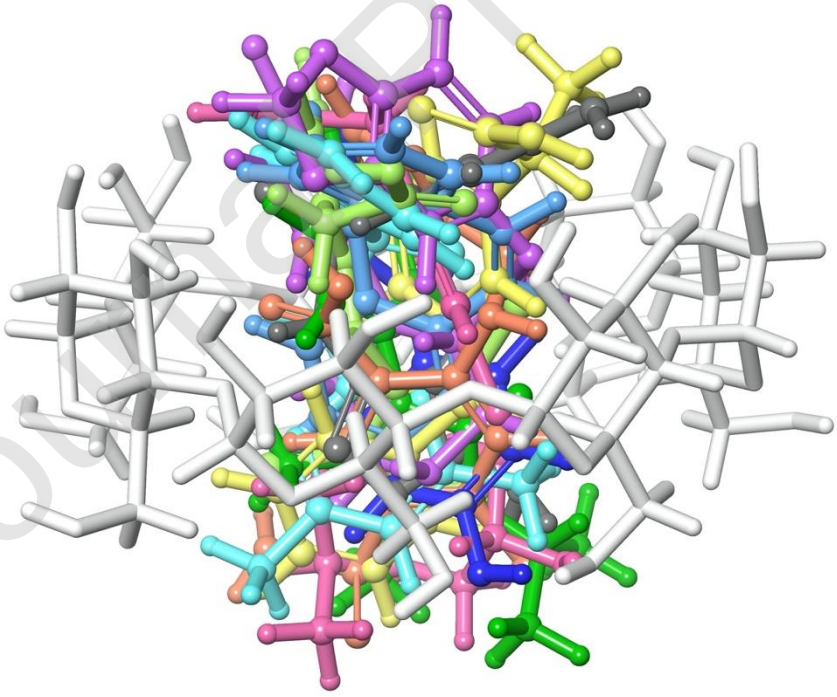


Figure 5. Docking results obtained in the complexation of pharmaceutical compound (showed as colored sticks) and β-CD (displayed in grey).

The performed calculations allow us to rationalize the most critical cases, namely, the pharmaceutical compounds with the lowest extraction yield (acetaminophen, propyphenazone, sulfamethazine and furosemide). The predicted binding energies for that four compounds range from -25.9 kcal/mol to -33.9 kcal/mol. To correctly interpret that numeric values, we underline that these binding energies are the less intense in the whole series. Indeed, we observe that compounds with the highest absorption correspond to the largest computed binding energies. This is particularly remarkable for the series of β-blockers. As illustrated in Figure 4, atenolol, propranolol and metoprolol exhibit a large elimination even if they present a measurable different hydrophobic nature (see associated log P values in Table S4). This finding is correlated to the theoretical outcomes, as all these molecules are associated to binding energies in the rage of -43.9/-45.0 kcal/mol, significantly more intense (more negative) that the reported values for acetaminophen, propyphenazone, sulfamethazine and furosemide. Therefore, even if a large binding energy does not linearly correlate with the final elimination, we demonstrated that it plays a pivotal role in the final sorption value.

3.3. The combined EPI-β-CD/pulsed light system

As stated before, the treatment with the EPI-β-CD polymer decreased the overall concentration of EPs mixture in water by 77 %. Representative chromatograms are provided as supplementary information (fig. S1). Treating the filtrate by PL raised the efficacy of the removal to 91 % (figs. 2-4). There are wide variations in removal efficacy among compounds, but at least 55 % abatement was achieved for the worst performing compound, sulfamethazine.

The complementary effect of PL can be better appreciated in those cases in which the concentration of the compound was high at the beginning of the PL treatment. The removal of anti-inflammatory compounds (fig. 2) and diuretics (fig. 4) raised from 68 and 55% respectively after polymer treatment to 91 and 97% respectively after additional PL treatment (see fig. 1). No compound was removed from water by less than 30 %. The poorest adsorbed compounds were propyphenazone (fig. 2), sulfamethazine (fig. 3) and furosemide (fig. 4). The complementary action of PL over the EPI-β-CD polymer treatment can also be observed here; increasing propyphenazone removal from 30 to 80 % and furosemide removal from 39 to 99 %, although sulfamethazine removal was only

increased from 38 to 55 %; being this compound the one that exhibited the poorest elimination from the 21 tested. Sulfamethazine has been identified as a photolysis refractive compound (Lian et al., 2015).

The elimination of contaminants by both methods has a practical ecological difference. The detection of lower concentrations of pollutants after polymer treatment means an absolute absence from water of those amounts retained, which would have consequences in lowering chemical oxygen demand and total organic carbon. In contrast, the reduction in the concentration of contaminants by PL would give place to by-products that could still be of ecological concern and complete mineralization cannot be warranted. Nonetheless, the highest pollutant abatement is accounted by the cyclodextrin polymer step. The high efficiency of this sequential system towards PhCs indicates its potential to treat *in situ* hospital wastewaters.

3.4. The contribution of PL technology to the combined process

When the focus is placed on the individual effect of PL, PL treatment abated the overall concentration of compounds remaining in water by 65 %. This percentage was calculated disregarding those compounds that were retained by the polymer by more than 90 % since their remaining concentrations were too low to get reliable values. The compounds considered for assessment of PL efficacy were the anti-inflamatories acetaminophen, diclofenac, indomethacin, ketoprofen, naproxen and propyphenazone; the lipid regulator bezafibrate; the antibiotics sulfamethazine and sulfamethoxazole; the anticonvulsant carbamazepine and the diuretics furosemide and hydrochlorothiazide. The order of decreasing sensitivity to direct photolysis was diclofenac, sulfamethoxazole, ketoprofen > furosemide > naproxen > hydrochlorothiazide > propyphenazone > indomethacin > acetaminophen > sulfamethazine > bezafibrate > carbamazepine.

The concentration of diclofenac, ketoprofen (fig. 2) and sulfamethoxazole (fig. 3) were decreased to undetectable levels by the PL treatment, and furosemide was almost completely eliminated (> 99%) (fig. 4), while a high level of elimination was reached for naproxen (fig. 2) and hydrochlorothiazide (> 85%) (fig. 4). On the other hand, carbamazepine (fig. 4) was the only compound completely refractory to PL action; this photoresistance has also been observed when treated with low-

or medium-pressure mercury lamps (Pereira et al., 2007). However, the drawback of the photolytic treatment is minimized in the context of the sequential process since the removal of carbamazepine by the EPI-β-CD polymer is already 79 %. The prospects for the potential use of PL in a real life scenario to destroy carbamazepine are not necessarily low since tests carried out in river waters (Matamoros et al., 2009) using a conventional light sources have shown enhanced degradation of this compound in comparison with pure water, likely due to action of oxidants generated from photolysis of the other compounds.

To the best of our knowledge, there are no previous reports about the use of PL for the degradation of pharmaceutical pollutants. Comparison of our results with those found for similar studies is limited due to significant differences in the emission spectrum of different light sources. The closest comparison that can be established is with medium-pressure mercury lamps because of their polychromatic output.

The use of PL to destroy PhCs is an innovative application of this technology. As commented before, EPs are not present in wastewater as single compounds, but as a mixture of different substances, therefore, PL technology can be especially suitable compared to other light technologies due to its wide-spectrum emission. For example, a low-pressure mercury lamp cannot degrade naproxen, which has poor light absorption above 250 nm, but can be degraded by 36 % by a medium-pressure mercury lamp (Pereira et al., 2007) and 87 % by PL; this comparison is very rough since it is not fluence-based. Other examples have been recently compiled by Yang et al. (2014). It should also be taken into account that industrial PL equipment's are capable to work at pulse repetition rates of 3 Hz (Kwaw et al., 2018), therefore 45 pulses could be delivered in just 15 seconds, which makes it a very time-efficient technology.

The sequence of photolytic susceptibility found in this work has some similitude with previous reports. Lekkerkerker-Teunissen et al. (2012) studied the degradation of carbamazepine, atrazine, diclofenac and sulfamethoxazole in deionized water by medium pressure mercury lamps light, which emits a broad spectrum light between 200-800 nm. Results showed that diclofenac and sulfamethoxazole were easily photolyzed by both light sources while concentrations of carbamazepine were not significantly reduced by any. The

rapid transformation of ketoprofen has also been reported for its direct photolysis under sunlight and simulated solar light (Matamoros et al., 2009).

Higher degradation levels may be reached by applying a higher number of light pulses and/or the incorporation of hydrogen peroxide in the frame of an advanced oxidation process (AOP). The first alternative may be ineffective for compounds that have shown to be recalcitrant at the tested treatment regime, but the latter alternative may be useful for all compounds. In such AOP, highly reactive hydroxyl radicals are generated by the photolytic splitting of hydrogen peroxide molecules. These radicals will oxidize contaminant molecules. This approach proved successful for the degradation of contaminant dyes in water when direct photolysis turned out to be ineffective (Martínez-López et al., 2019).

3.5. Reusability of the EPI-β-CD polymer

The reusability of the EPI-β-CD polymer was evaluated using ibuprofen (2 mg/L) as a model compound. The capability of the polymer to eliminate the contaminant drops as the contact time advances (fig. 6A), which is expected since the adsorption sites are saturated during the process. The polymer was regenerated once saturated in order to be reused, the results for each of ten use cycles tested for the first 10 minutes of contact time (fig. 6B), show that the polymer can be reused at least up to 10 times without a significant loss of its capacity to eliminate the model contaminant. The original polymer was able to eliminate 87 % of ibuprofen and it was still able to eliminate 74 % of ibuprofen when used 10 times. A linear extrapolation of data allows estimating that the polymer can be used 23 times before declining its adsorption capacity below 50 %. While the result can be dependent of the model compound selected for the test, it has general validity regarding the resistance of the adsorption capacity of the polymer, towards the buffer used to elute the compounds that can be adsorbed by its structure. This finding is beneficial from the economical point of view at full-scale operation because delays the requirement for replacement of the adsorbent, saving money and working hours.

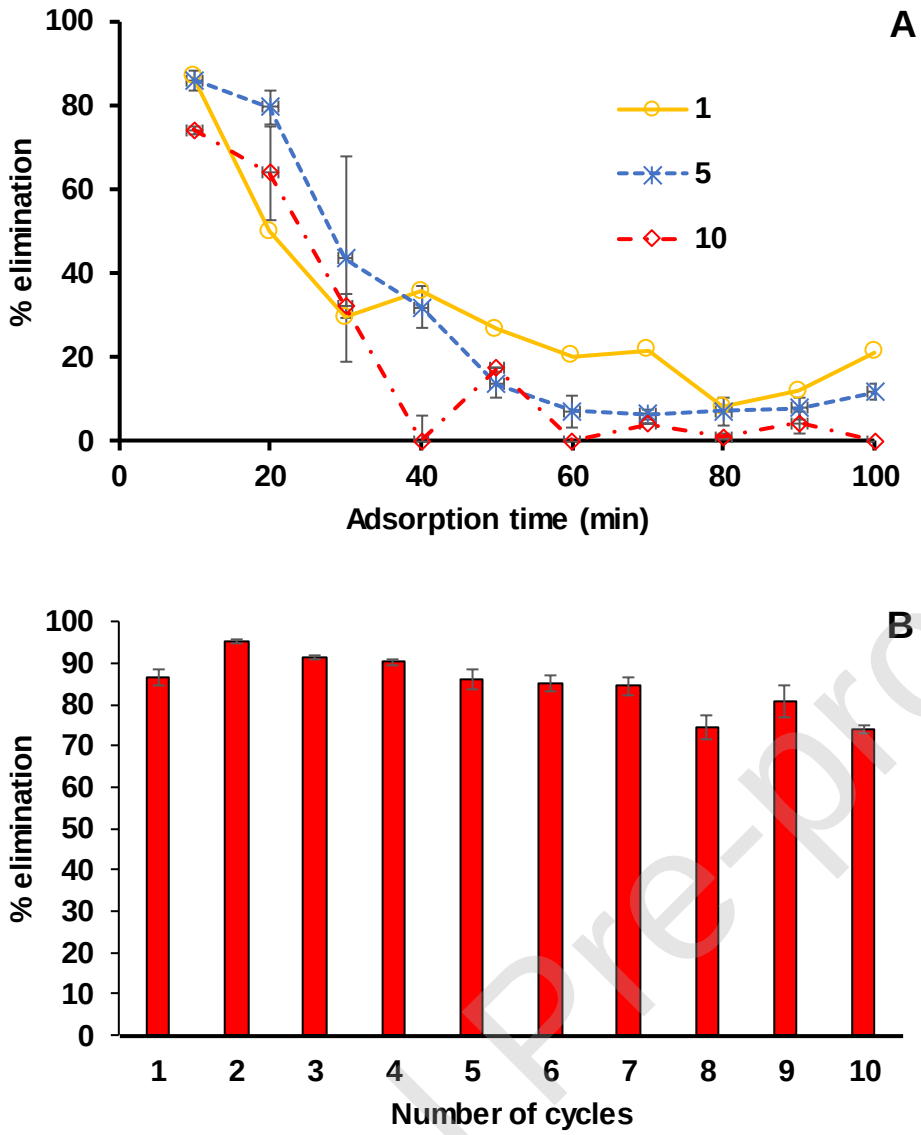


Figure 6. Reusability of an epichlorohydrin cross-linked β-CD polymer based on the elimination of ibuprofen from water. A: Percentage of ibuprofen elimination as function of adsorption time for selected cycles. B: Percentage of ibuprofen elimination after 10-min contact time.

3.6. Acute toxicity test

The decrease of the concentration of pollutants in water leads to think that the toxicity of the final solution is also lower. This could be valid when a separation process such as encapsulation in CD polymers is used but not necessarily when the photolytic process is applied, due to the potential toxicity of degradation compounds as it has been observed for other pollutants (Zhou et al., 2020). Therefore, the effect of the sequential cyclodextrin polymer/PL process on the

toxicity of pollutants was assessed using ibuprofen as a proof of concept, to treat *in situ* hospital wastewaters. The 2 mg/L ibuprofen solution in water was toxic and the polymer treatment gave place to an effluent with no toxicity (table 3). The treatment of this effluent with PL did not modify its toxicity but its evaluation was deserved since it could have increased the toxicity if the low amounts of ibuprofen remaining are decomposed to toxic by-products that could have increased effluent toxicity.

Table 3. Toxicity results of water containing Ibuprofen against the *crustacean Thamnocephalus platyurus*, after different removal treatments.

Water treatment	EC_{50}	TUs	Toxicity
$K_2Cr_2O_4$	4.17	24.0	Acute toxic
Buffer acetate	4.17	24.0	Acute toxic
Ibuprofen	27.1	3.7	Toxic
Ibuprofen after polymer	N.A.	0.0	Non toxic
Ibuprofen after polymer and PL	N.A.	0.0	Non toxic
Ibuprofen in acetate buffer after PL treatment	4.17	24.0	Acute toxic

TU < 1 (non toxic); 1 ≤ TU < 10 (toxic); 10 ≤ TU < 100 (acute toxic); 100 ≤ TU (very toxic).

Samples eluted from the polymer and then treated with PL showed acute toxicity, but this could have been due to an effect of the buffer since the toxicity of the buffer alone yielded the same results. This has a minor impact on the system since the buffer is intended for reuse in regenerate the polymer.

4. Conclusion

PhCs were consistently detected in WWTPs from Región de Murcia (Spain). In order to eliminate them, a sequential process consisting in the adsorption of PhCs by EPI-β-CD polymer and a photolytic degradation of those amounts still remaining in the water by PL was designed and tested. The EPI-β-CD polymer abated the concentration of PhCs by 77 % after 30 minutes' contact time, with 71 % removal already occurring during the first five minutes. We demonstrated that retention depends on a several combined parameters between the sorbent and the drug to be eliminated, including polarity, size, stereochemistry and the specific

interactions between drugs and amphiphilic three-dimensional polymeric network. The performed calculations show that the binding energies can be used to predict the relative order of retention yield. Pollutant degradation was raised to 91 % after applying a complementary photolysis by pulsed light. The photolytic process was improved by a previous use of a CD-polymer for removal water turbidity and PhCs concentration, saving time (100 min), energy (0.04 kW) and costs (0.958 € per each removal cycle), resulting in consequence a positive balance. The polymer can be reused at least 10 times for ibuprofen (model compound) retention. The ecotoxicity of a 2 mg/L ibuprofen solution is completely eliminated by treatment with the EPI-β-CD polymer and it's not increased by the PL treatment. This work opens new possibilities of study in the field of the elimination of emerging pollutants from water, and especially in the elimination of PhCs.

Credit statement

T.G.-M.: polymer treatment of waters, C.L.-A.: Ecotoxicity analysis, V.M.G.-L.: experimental design, data analysis and manuscript writing, I.M.-A.: Ecotoxicity data treatment, M.A.: interpretation and writing results from WWTPs, S.M-L.: collection and analysis of water samples from WWTPs, N.M.: Preparation of mix of pharmaceutical compounds and extraction before chromatographic analysis, S.P.: Validation of analytical method for pharmaceutical analysis by liquid chromatography MS/MS spectrometry, D.B.: Conceptualization and LC-MS/MS writing, P.F.: Reusability assays, P.C.: Assay resources and writing, J.P.C-C.: theoretical calculations and analysis, M.I.F.: Pulsed light assays, E.N.-D.: Methodology and writing, J.A.G.: Experimental design and revision of the article.

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.

Acknowledgements

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Appendix A. Supplementary data.

Supplementary material related to this article is supplied as tables S1-S4.

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