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PROCESSES OF DISTRIBUTION OF PHARMACEUTICALS IN SURFACE FRESHWATERS: IMPLICATIONS FOR RISK ASSESSMENT

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Abstract

The global consumption and production of pharmaceuticals is increasing concomitantly with concern regarding their environmental fate and effects. Active pharmaceutical ingredients are mainly released into the aquatic environment through wastewater effluent discharge. Once in the environment, pharmaceuticals can undergo processes of natural attenuation, i.e. dilution, sorption, transformation, depending on physico-chemical properties of the compound, such as water solubility, lipophilicity, vapour pressure, and environmental conditions, such as pH, temperature and ionic strength. A major natural attenuation process is the sorption on dissolved organic matter, colloids, suspended solids and sediments, which in turn control pharmaceuticals distribution, residence time and persistence in aquatic systems. Here we review studies of sorption capacity of natural sorbents to pharmaceuticals. These report on the importance of several environmental and sorbent-specific properties, such as the composition, quality, and amount of the sorbent, and the environmental pH, which determines the speciation of both the sorbent and compound. The importance of accounting for distribution processes on freshwater sorbents for any determination of environmental concentrations of pharmaceuticals is apparent, while the reliability of surrogate standards for measuring dissolved organic matter (DOM) distribution is evaluated in the context of the need for robust environmental risk assessment protocols.

Keywords

Pharmaceuticals; sediments; sorption; dissolved organic matter; suspended solids; environmental risk assessment.

1. Introduction

The global pharmaceuticals market is expanding year on year, leading to their presence in sewage effluent (Gardner et al. 2012, 2013), and subsequent concerns regarding the ecosystem impact of these emerging contaminants. Active pharmaceutical ingredients have received attention, since reports of endocrine disruption in fish from 17α-ethinylestradiol in the ng L^{-1} range (Purdom et al. 1994; Sumpter and Jobling 1995), secondary poisoning of Indian vulture populations caused by the non-steroidal anti-inflammatory drug diclofenac (Swan et al. 2006) and antibiotic resistance (Kookana et al. 2014). Improvements in analytical technologies mean that many new compounds can be detected in environmental matrices at very low concentrations (< 1 ng L^{-1}) and the increased number of studies demonstrating the presence of pharmaceuticals in surface and groundwater worldwide have been undertaken alongside evidence of ecotoxicological effects (Nikolaou et al. 2007; Brausch et al. 2012).

Pharmaceuticals comprise a large and diverse class of compounds used for the prevention, cure or treatment of diseases in humans and animals, and include about 1450 molecules differing in physicochemical and biological properties and mode of action (Kinch et al. 2014). Although clinical testing ensures that human biological effects are well known (Ågerstrand et al. 2015), uncertainties exist concerning the environmental risk posed by pharmaceuticals. This is due to limited knowledge concerning their fate and behaviour in wastewaters and the environment, their uptake, metabolism and excretion, pharmacokinetics, in wildlife, and their target affinity and functional effects, pharmacodynamics, in non-target species (Arnold et al. 2014; Verbruggen et al. 2018). Pharmaceuticals which are persistent, bioavailable, toxic and mobile, i.e. high solubility, are of greatest concern. Furthermore, complexation, or conjugation, of pharmaceuticals

and the generation of metabolites during sewage treatment, or in the environment, create further uncertainty regarding environmental exposure and ecotoxicological effects (Boxall et al. 2012).

The principal source of human pharmaceuticals to the environment is via discharge of treated and untreated wastewater (Daughton and Ternes 1999; Kookana et al. 2014; Malik et al. 2015). Despite the high degree of degradability of some pharmaceuticals, continuous inputs can result in pseudo-persistent behaviour (Grenni et al. 2013). Industrial manufacturing plants are also considered important point sources of pharmaceuticals to the environment (Cardoso et al. 2014; Larsson 2014), as well as livestock farming and aquaculture, which are significant sources of veterinary pharmaceuticals (Carmosini and Lee 2009; Shimizu et al. 2013; Song and Guo 2014). Fig 1 depicts the known environmental pathways of pharmaceuticals (Heberer 2002; Benotti et al. 2009).

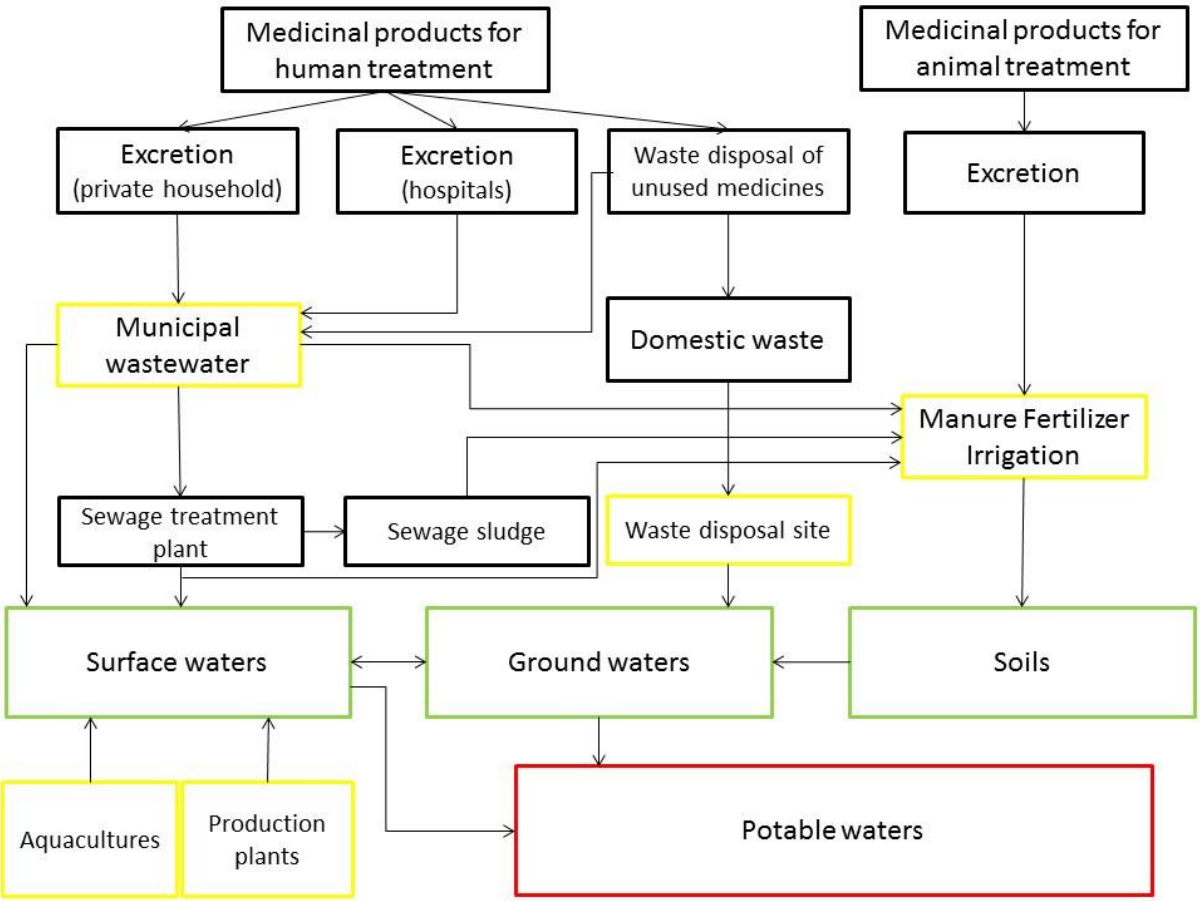

Fig 1. Sources and pathways of pharmaceuticals to the environment and the intermediate steps encountered between the point source and the receiving environmental compartment (Heberer 2002). Yellow boxes depict the main point sources to the environment; green boxes represent the receiving environmental compartments; the red box indicates a direct source of human exposure.

Once in the environment, pharmaceutical concentrations may be reduced by physical, biological or chemical processes. These processes, summarised in Fig 2, include dilution, transformation such as photo-degradation, bio-degradation, and hydrolysis, and sorption (Gurr and Reinhard 2006). Natural attenuation may reduce environmental concentrations, and therefore potential toxicity of chemicals (Tappin et al. 2012, 2014; West and Rowland 2012). Its extent determines the fate of contaminants in the environment, namely occurrence, distribution, and bioavailability (Lin et al. 2010).

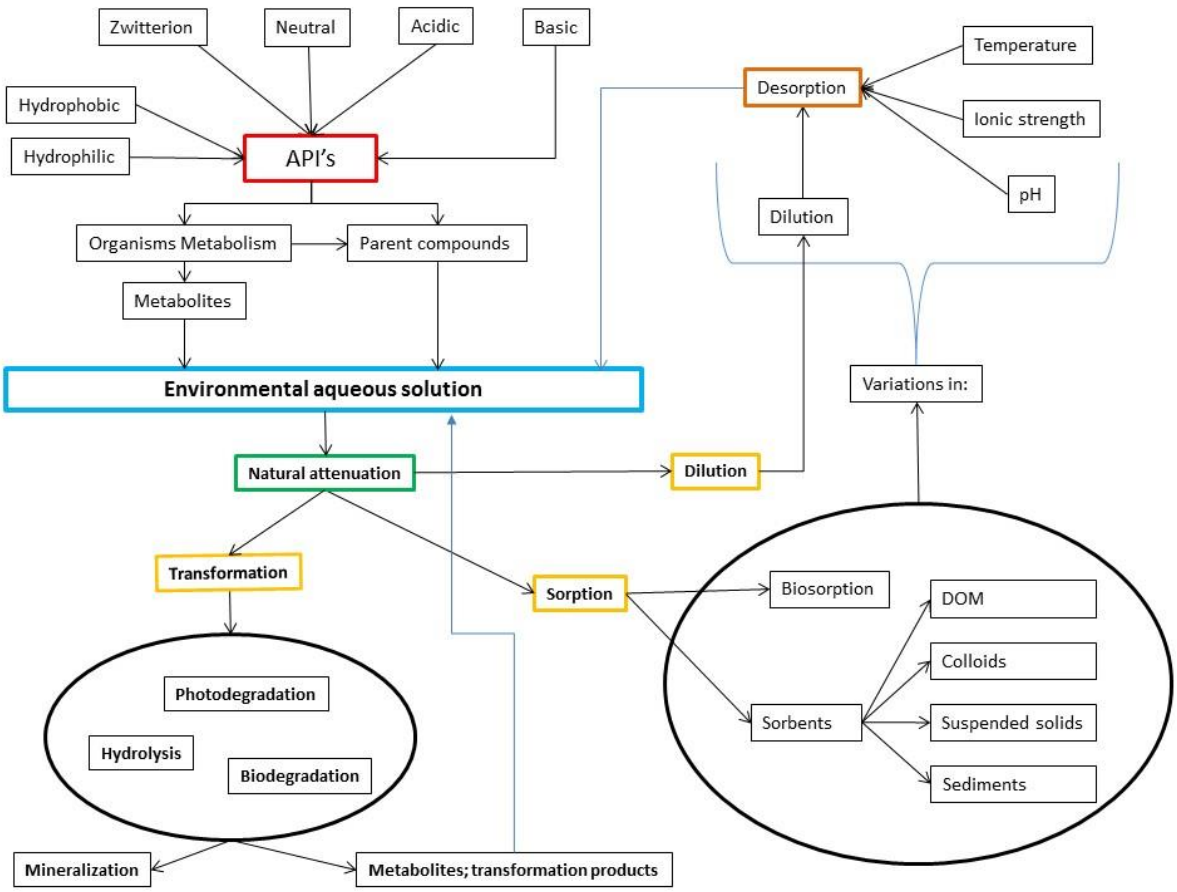

Fig 2. Pathways representing the environmental fate of pharmaceuticals. The red box refers to pharmaceutical characteristics; the blue box depicts the environmental receiving compartment; the yellow boxes serve as subdivision of the three main attenuation mechanisms; the orange box indicates the desorption factors; the pale blue coloured arrows are dissolution pathways; DOM is Dissolved Organic Matter.

Attenuation of pharmaceuticals through partitioning onto sorbents in surface waters can be significant in controlling distribution, residence time and persistence in aquatic systems (Lützhøft et al. 2000); as a result ecotoxicological effects might be either reduced, as the pharmaceutical is less bioavailable, or increased through bioconcentration (Ra et al. 2008). The extent and reversibility of partitioning depends on both the pharmaceutical and sorbent surface characteristics (Delle Site 2001). The degree of partitioning is expressed by the partition coefficient (K), which is the particulate : solution concentration ratio of the pharmaceutical. The pharmaceutical functionality; basic, acidic, neutral or zwitterion, is critical in controlling its fate. For ionisable compounds, where the degree of ionization is pH-dependent, expressed by the acid dissociation constant,

pK_a. Fig 3 demonstrates the ionisation behaviour of molecules representing basic, acidic and zwitterion pharmaceuticals at pH 5 – 9. Basic compounds are fully ionised at the lower pH and the neutral fraction abundance increases above pH 7 (Fig 3A), whilst acidic pharmaceuticals demonstrate converse behaviour (Fig 3B). The zwitterion, ofloxacin, contains at least one charge over the pH range (Fig 3C). These pH-related changes in the abundance of each species affect their distribution in aquatic environments.

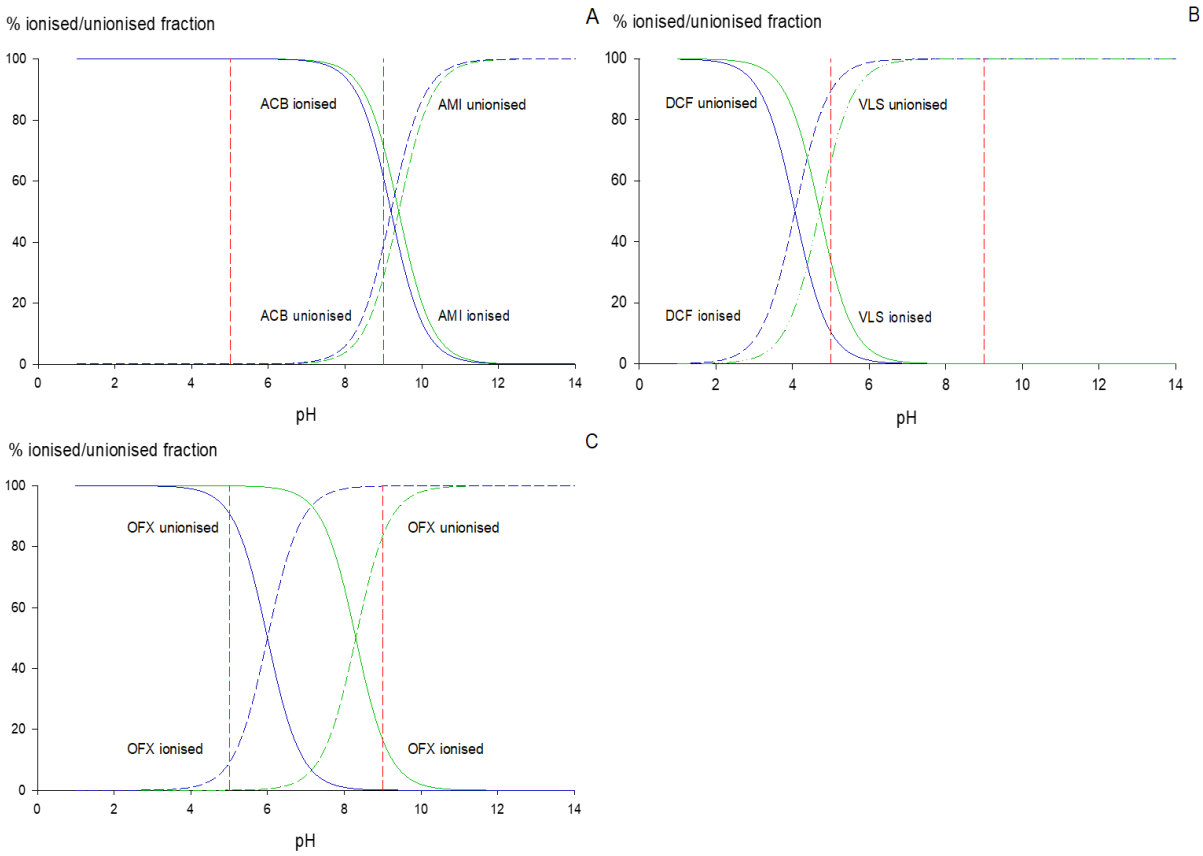

Fig 3. pH-dependent ionization for A. two basic compounds, amitriptyline (AMI) (pKa 9.4) and acetobutol (ACB) (pKa 9.2) B. two acidic compounds, diclofenac (DCF)(pKa 4.0) and valsartan (VLS)(pKa 4.7). C. the zwitterion ofloxacin (OFX) (pKa basic 8.3, acidic 6.0). All the functionalities show an unionised fraction environmental pH range (red lines).

The main sorbents in aquatic environments are dissolved organic matter (DOM), colloids, suspended solids and sediments (Fig 2).

1.1 Dissolved organic matter

DOM is a biogeochemical product which interacts with organic pollutants in water (Leenheer and Croué 2003). It can be derived from natural or anthropogenic sources and is present in natural waters at concentrations ranging from 0.1 mg L^{-1} in groundwater to above 300 mg L^{-1} in wastewater (Leenheer and Croué 2003; Tchobanoglous et al. 2003). DOM has not been completely characterized but is regarded as a mixture of aliphatic and aromatic compounds with some predominant chemical functionality, including hydroxyl, carboxyl, amido and keto groups (Leenheer and Croué 2003). For experimental purposes, environmental DOM is physically filtrated from water, typically 0.45 or 0.2 μm membranes, and chemically fractionated (e.g. via sorption and elution from resins) in order to obtain operationally-defined DOM fractions, namely hydrophobic or hydrophilic, and the acidic, basic or neutral sub-classes (Filella 2009; Maoz and Chefetz 2010). Further classification is based on fluorescence excitation-emission matrix patterns, which show distinct "protein-like" and "humic-like" peaks (Hudson et al. 2007). DOM in aquatic environments can be derived from *in situ* autochthonous sources by bacterio-plankton activity, or introduced via carbon recycling (Michael-Kordatou et al. 2015).

1.2 Colloids

Colloids are often defined as particles in the size range between 1nm and 1 μm; they include clays such as layered silicates, metal oxides such as Fe- and -Al- hydroxides, organic material such as humic acids, proteins, and bio-colloids such as bacteria, viruses, and are ubiquitous in the environment (Zhou et al. 2007). Colloids are formed and transported to surface waters by weathering and biological processes. Their large specific surface area and sorption capacity play a crucial role in the speciation, bioavailability and transport of substances in the aquatic environment (Zhou et al. 2007; Xing et al. 2015).

1.3 Suspended solids and sediments

Suspended solids are a source of material that, in the case of contaminant loads, becomes a medium for accumulation in the sediment compartment (Lahti and Oikari 2011). Sediments are defined as settled material derived from weathering, erosion of minerals, and decay of organic matter, and transported by the action of the wind, water or ice, and the force of gravity acting on the suspended solids. Sediments provide an important environmental surface for partitioning processes; and therefore, are of importance in determining the fate of chemicals in the environment.

1.4 Importance of sorption in risk assessments

Sorption processes are important in determining predicted environmental concentrations for environmental risk assessments. For example, the OSPAR convention states that compounds with distribution coefficient (log K_{ow}) above 4.5 are screened for persistence, bioaccumulation and toxicity, following European Technical Guidance on Risk Assessment (European Comission Joint Research Centre, 2003). The European Medicines Agency guidelines for the environmental risk assessment of pharmaceutical compounds proposes a Phased approach. Phase 1, a pre-screening worst-case scenario, considers the parent compound only, irrespective of mode of administration, metabolism and excretion (EMA 2006). If the predicted environmental concentration is above 0.01 µg L^{-1}, Phase 2 entails analysis of the environmental fate and effects, although a tailored environmental risk assessment could be triggered below this threshold if the pharmaceutical is shown to affect reproduction. A PBT assessment is required at Phase 1 for APIs that have a Log K_{ow} > 4.5. Phase 2 is a tiered phase, comprising Tiers A and B. Tier A involves the ready biodegradability test (OECD 1992) followed by a water-sediment distribution study if the analyte is shown to be persistent (OECD 2000). Toxicity tests are also performed to allow for a Predicted No Effect Concentration to be estimated.

If the "Predicted Environmental Concentration" : "Predicted No Effect Concentration" ratio indicates a risk, a Tier B assessment should be conducted where the predicted environmental concentration for surface water is refined to include information from wastewater treatment plant modelling using the SimpleTreat model (EMA 2006), where a factor is applied to allow for the partitioning of the chemical.

A terrestrial environmental risk assessment is triggered at Tier B if the K_{oc} of the active pharmaceutical ingredient is >10,000. Fish bioconcentration studies at Tier B are required at Log K_{ow} > 3 and a sediment toxicity assessment is required for pharmaceuticals where 10 % of the applied radioactivity adsorbs to sediment in the water-sediment transformation study conducted at Tier A (EMA , 2006).

The distribution of a pharmaceutical between the particulate and dissolved phases is therefore critical in determining its environmental fate, including mobility, persistence, bioavailability and subsequent toxicity. It is also critical for defining whether a terrestrial- or sediment-based environmental risk assessment is required as part of the marketing application in Europe. There is currently no study that compiles the available partitioning data for pharmaceuticals, nor identifies the significant data gaps and relates it to pharmaceutical environmental fate. This review evaluates, for the first time, published information regarding the partitioning of pharmaceuticals to DOM, colloids, suspended solids and sediments in natural surface aquatic environments and relates this to risk assessment processes.

2. Meta-analysis

2.1. Data collection

Published studies on the distribution of pharmaceuticals in freshwater environments were screened for the collection of data, documenting the source and concentration of the sorbents used in the experiments, pH, and pharmaceutical partition coefficients along with physicochemical parameters such as pK_a and log K_{ow}. Data sources included the open chemistry database PubChem (https://pubchem.ncbi.nlm.nih.gov/), available scientific literature and environmental fate estimation program software (EPI Suite™, Table 1, Table 2, Table 3, Table 4).

Fig 4 shows a graphical comparison of the number of articles, pharmaceuticals, metabolites and transformation products, and compounds per functionality investigated for each sorbent. Nine articles about sorption processes of pharmaceuticals to DOM, mostly reference materials but also some wastewater-derived DOM (Table 1), were identified (Lützhøft et al. 2000; Yamamoto et al. 2003; Bai et al. 2008; Carmosini and Lee 2009; Kim et al. 2010; Maoz and Chefetz 2010; Ding et al. 2013; Martínez-Hernández et al. 2014; Peng et al. 2014).

The total number of pharmaceuticals studied was 20, comprising 1 neutral species, 3 acidic, 3 basic, 13 zwitterions, and 3 metabolites. The experimental pH ranged from 3 to 8, which is a critical parameter regarding the charge present on the pharmaceutical molecule and its subsequent fate.

Four articles related to the partitioning of pharmaceuticals to colloids; extracted from samples of river water, groundwater, seawater and wastewater (Table 2) (Holbrook et al. 2004; Maskaoui et al. 2007; J. L. Zhou et al. 2007; Maskaoui and Zhou 2010). Here, 10

compounds were studied comprising 2 neutral, 3 acidic, and 5 basic species, with experimental pH ranging from 6.4 to 8.5.

Fourteen articles referring to suspended solids and sediment partitioning were identified, with 70 compounds studied (Löffler et al. 2005; Stein et al. 2008; Ra et al. 2008; Yamamoto et al. 2009; Lin et al. 2010; Maskaoui and Zhou 2010; Githinji et al. 2011; Lahti and Oikari 2011; Zhou and Broodbank 2014; Martínez-Hernández et al. 2014; Paul et al. 2014; Svahn and Bjorklund 2015; Li et al. 2015; Al-Khazrajy and Boxall 2016). Of the compounds studied, 4 were metabolites and 8 were transformation products; 20 were acidic, 38 basic, 7 neutral, and 3 were zwitterions across a pH range of 3.5 to 10 (Table 3, Table 4).

Suspended solids and sediments dominated the studies on pharmaceuticals (70), where a number of metabolites and transformation products were also investigated. Basic compounds were most studied in suspended solids and sediments (38), followed by the acidic (20), neutral compounds (7), and zwitterions (3). The distribution to colloids was investigated for 5 basic, 3 acidic and 2 neutral compounds. The DOM distribution studies included the largest amount of zwitterion compounds (13), followed by acidic (3), basic (3) and neutral (2).

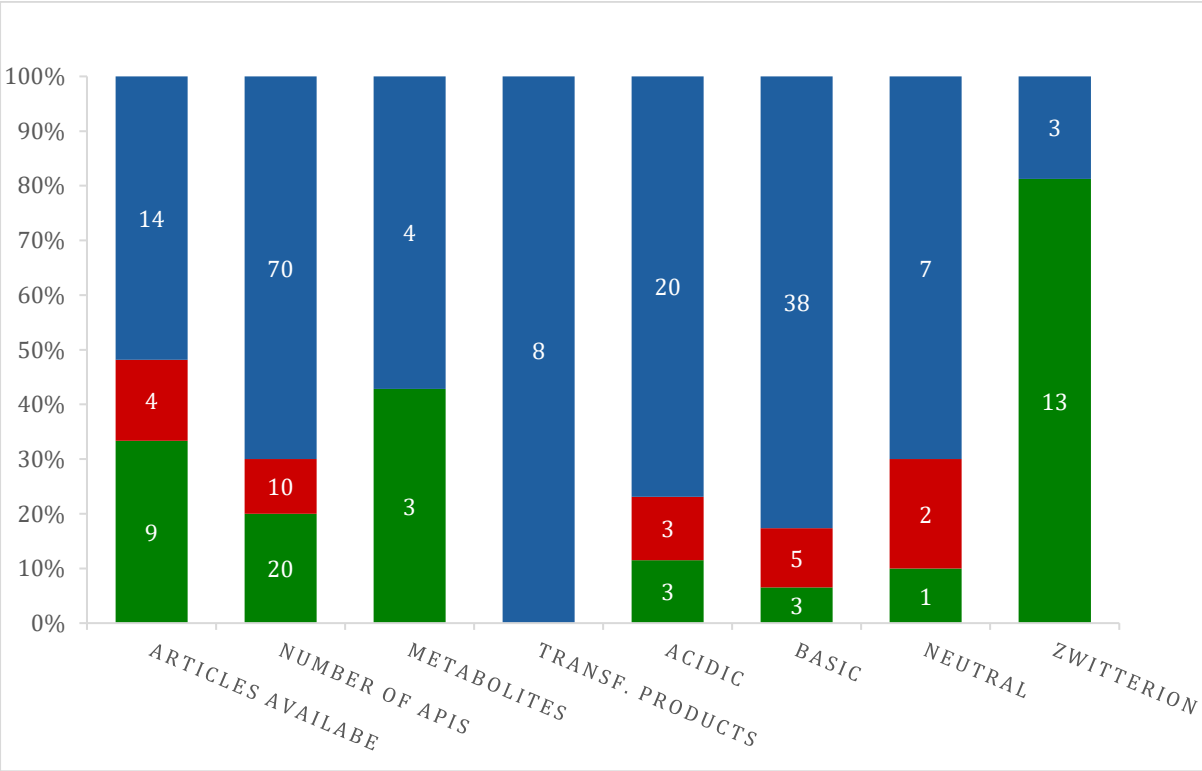

Fig 4. A comparison of published articles on pharmaceuticals partitioning to DOM (green), colloids (red), suspended solids and sediments (blue). The columns, from left to right, refer to the number of articles, the number of studied active pharmaceutical ingredients (APIs), metabolites identified, transformation products identified, classification according to pharmaceuticals' functionality: acidic, basic, neutral and zwitterion.

The measured organic carbon-water distribution values (K_{oc}) of each compound were plotted against the corresponding octanol-water distribution coefficient values (K_{ow}) for the three sorbents; i.e. DOM, colloids, and suspended solids and sediments. No relationship was apparent which deviates from correlations for non-polar organics. However, selecting only the neutral pharmaceuticals and plotting organic carbon normalised log K_{oc} against corresponding log K_{ow} for each sorbent did show a linear relationship for DOM (R^2=0.846), albeit for a limited number of data (n=5). No significant relationship was observed for other sorbents (Fig 5).

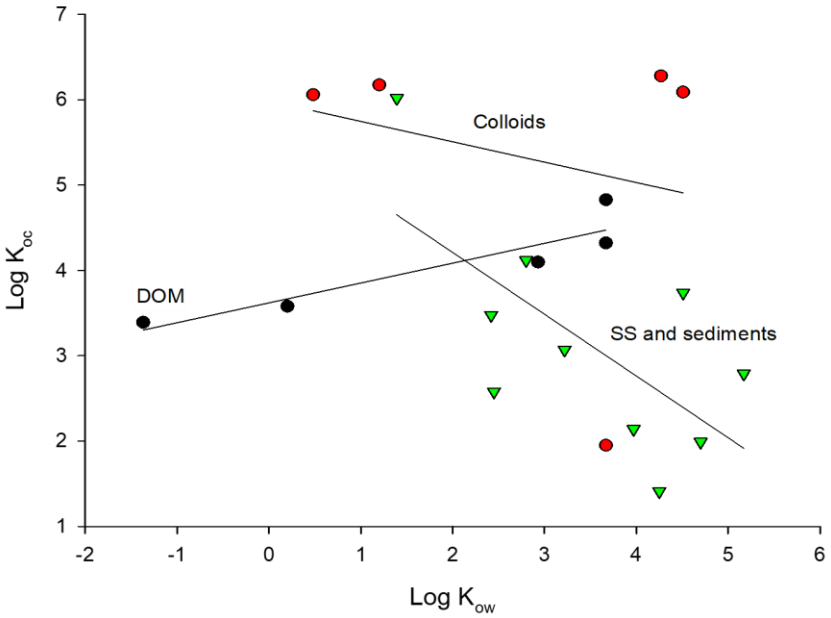

Fig 5. Organic carbon-water (K_{oc}) distribution values of the neutral compounds plotted against the correspondent octanol-water (K_{ow}) distribution coefficient value for each sorbent, namely dissolved organic matter (DOM) (black dots) R^2=0.846, colloids (red dots) R^2=0.055, suspended solids and sediments (green triangles) R^2=0.450; Showing a significant relationship only for DOM, though for a very limited number of data (5).

2.2. Partitioning to dissolved organic matter

Yang et al. (2011) reported a weak positive linear relationship (R^2= 0.509) between the freshwater total concentration of five groups of antibiotics and DOM. Furthermore, Lützhøft et al. (2000) demonstrated an inverse relationship between the concentration of "free" pharmaceuticals in solution and DOM concentration, limiting bioavailability and possibly toxicity (Urrestarazu Ramos et al. 1998; Rowett et al. 2016), but increasing environmental persistence. These two studies highlight both the lack of available data as well as a potentially significant role for DOM in determining environmental exposure to pharmaceuticals.

2.2.1 Dissolved organic matter composition

The composition of DOM is source-dependent. For example, anthropogenic wastewater is mainly composed of proteinaceous matter, whilst freshwater DOM is dominated by

humic substances (Hudson et al. 2007; Hernandez-Ruiz et al. 2012). The partitioning of the β-blocker propranolol on DOM derived from river and lake surface water generated log K_{dom} values ranging from 3.9 - 5.2 L kg^{-1} (Table 1), with protein-like DOM associated with lower values and humic-like substances exhibiting highest log K_{dom} (Peng et al., 2014). Similar results were obtained for the anti-epileptic drug, carbamazepine, which showed most extensive partitioning to humic substances, including fulvic acids from landfill leachate, river water and Amherst humic acid, with log K_{dom} between 3.41 and 5.04 L kg^{-1} (Table 1)(Hernandez-Ruiz et al. 2012). However, complexation of carbamazepine with tryptophan-like DOM was also significant, suggesting an important role for anthropogenic organic matter in the transport and transformation of such pharmaceuticals (Wang et al. 2016). Since carbamazepine is a neutral compound, hydrophobic sorption mechanisms to humic acid were proposed (Bai et al. 2008).

2.2.2 Organic matter reference standards as a proxy for partitioning of pharmaceuticals

The use of reference standards of humic DOM as a proxy for measuring partitioning of pharmaceuticals to DOM may result in an overestimation of the binding capacity. Carmosini and Lee (2009) and Peng et al. (2014) investigated the partitioning of the zwitterion, ciprofloxacin, to contrasting DOM types at different pH and ionic strengths. The DOM included Leonardite standard humic acid, Pahokee Peat humic acid, Pahokee Peat II standard fulvic acid and Elliott Soil II standard fulvic acid. Other DOM types were obtained from digested and undigested municipal biosolids, municipal wastewater effluent, and beef industry lagoon wastewater. The wastewater-derived DOM showed much less affinity for ciprofloxacin than the reference humic standards. Furthermore, the former did not show a pH-sorption correlation as in the latter DOM type, which suggests that a mechanism other than ion exchange was controlling the sorption process. These interactions are likely driven by the more aliphatic protein composition of the

wastewater-derived DOM than the aromatic humic DOM of the reference standards, exhibiting a different sorption characteristic and cation exchange capacity. Such variation in partitioning has also been observed for pharmaceuticals, carbadox, tetracycline, and lincomycin, tested using reference standards such as Leonardite humic acid and Aldrich humic acid, where the former showed greatest sorption capacity, probably as a result of more interaction sites being available (Table 1) (Ding et al., 2013).

1 **Table 1** Dissolved organic matter (DOM) partition coefficient (Log K_{DOM}) for pharmaceuticals, sources and type of organic matter,
2 experimental concentration and pH. Legend: * metabolites; N.A. not available.

Compound	Type	pKa	$LogK_{ow}$	Source of DOM	DOM type	Concentration [mg/L]	pH	Log K_{DOM} [L/kg]	Reference	Year
17α – ethynylestradiol	acidic	10.21	3.67	Reference standards; river;	Aldrich humic acid	2, 10	7	4.78	Yamamoto et al.	2003
					Suwannee river humic acid	2, 10	7	4.80	Yamamoto et al.	2003
					Suwannee river fulvic acid	2, 10	7	4.55	Yamamoto et al.	2003
					Nordic fulvic acid	2, 10	7	4.63	Yamamoto et al.	2003
					Alginic acid	2, 10	7	3.23	Yamamoto et al.	2003
					Dextran	2, 10	7	3.04	Yamamoto et al.	2003
					Tannic acid	2, 10	7	5.22	Yamamoto et al.	2003
Albendazole	zwitterion	3.37, 9.93	3.07	Reference standards; synthesis;	Aldrich humic acid	5000-15000	7	3.52	Kim et al.	2010
					hydroxypropyl-b-cyclodextrin	20000	7	2.96	Kim et al.	2010
					POPC liposome	480-1700	7	3.77	Kim et al.	2010
					sodium dodecyl sulfate	10000-25000	7	3.02	Kim et al.	2010
Amino-fenbendazole	Zwitterion	6.94, 10.65	3.17	Reference standards; synthesis	Aldrich humic acid; hydroxypropyl-b-cyclodextrin; sodium dodecyl sulfate; 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; lyposome;	5000-15000	7	n. a.	Kim et al.	2010
Carbadox	Basic	1.98	n. a.	Reference standards;	Leonardite	46.4	8	3.52	Ding et al.	2013
					Humic acids	79.4	8	3.26	Ding et al.	2013
Carbamazepine	Neutral	13.9	2.93	Landfill leachate	FA	25	7	3.41 to 5.04	Bai et al.	2008
				Amherst humic acid	HA	25	7	4.58 - 4.82	Bai et al.	2008
				Wastewater and Suwannee river.	n. a.	8	n. a.	n. a.	Hernandez-Ruiz et al.	2012
				Sewage sludge	Bulk DOM	1000	8	2.64	Maoz and Chefetz	2010
Ciprofloxacin	Zwitterion	5.9; 8.9	0.4	Digested and undigested biosolids; treated wastewater;	≤1000 Da; ≥1000 Da fraction;	25	n. a.	n. a.	Carmosini and Lee	2009

				beef lagoon wastewater; humic acids reference standards;						
Fenbendazole	Zwitterion	5.12, 12.72	3.85	Reference standards; synthesis;	Aldrich humic acid	5000-15000	7	3.06	Kim et al.	2010
					hydroxypropyl-b-cyclodextrin	20000	7	3.25	Kim et al.	2010
					POPC liposome	480-1701	7	3.23	Kim et al.	2010
					sodium dodecyl sulfate	10000-25000	7	2.92	Kim et al.	2010
Fenbendazole sulfone*	Zwitterion	3.41, 11.12	2.17	Reference standards; synthesis;	Aldrich humic acid; hydroxypropyl-b-cyclodextrin; sodium dodecyl sulfate; 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; lyposome;	5000-15000	7	n. a.	Kim et al.	2010
Flubendazole	Zwitterion	3.6, 9.6	2.91	Reference standards; synthesis;	Aldrich humic acid	5000-15000	7	2.60	Kim et al.	2010
					hydroxypropyl-b-cyclodextrin	20000	7	2.08	Kim et al.	2010
					POPC liposome	480-1702	7	n.a.	Kim et al.	2010
					sodium dodecyl sulfate	10000-25000	7	2.04	Kim et al.	2010
Flumequine	Zwitterion	6.4	1.72	Reference standard;	Aldrich Humic acid	1, 5, 12.5, 25, 50	3	3.44	Lutzhoft et al.	2000
						1, 5, 12.5, 25, 50	4	3.65	Lutzhoft et al.	2000
						1, 5, 12.5, 25, 50	5	4.23	Lutzhoft et al.	2000
						1, 5, 12.5, 25, 50	6	4.39	Lutzhoft et al.	2000
						1, 5, 12.5, 25, 60	7	4.23	Lützhøft et al.	2000
						1, 5, 12.5, 25, 50	8	4.36	Lützhøft et al.	2000
Ibuprofen	Acidic	4.41	3.5	Wastewater and Suwannee river.	n. a.	8	n. a.	n. a.	Hernandez-Ruiz et al.	2012
Lincomycin	Basic	7.6	0.2	Reference standard	Leonardite humic acid	46.4	8	3.96	Ding et al.	2013
					Aldrich humic acid	79.4	8	3.20	Ding et al.	2013
Naproxen	Acidic	4.2	3.18	Sewage sludge	Hydrophobic acid, basic, and neutral fractions; hydrophilic acid, basic, and neutral fractions.	1000	8	negligible	Maoz and Chefetz	2010
Oxfendazole*	Zwitterion	4.13, 11.79	1.63	Reference standards; synthesis;	n. a.	5000-15000	7	n. a.	Kim et al.	2010
Oxolinic acid	Zwitterion	6.9	0.68	Aldrich humic acids;	Humic acids;	1, 5, 12.5, 25, 50	3	3.87	Lützhøft et al.	2000
						1, 5, 12.5, 25, 50	4	4.00	Lützhøft et al.	2000
						1, 5, 12.5, 25, 50	5	4.37	Lützhøft et al.	2000
						1, 5, 12.5, 25, 50	6	4.50	Lützhøft et al.	2000
						1, 5, 12.5, 25, 50	7	4.48	Lützhøft et al.	2000

						1, 5, 12.5, 25, 50	8	4.37	Lützhøft et al.	2000
p-hydroxyfenbendazole*	Zwitterion	5.49, 9.48, 11.38	3.37	Reference standards; synthesis;	n. a.	5000-15000	7	n. a.	Kim et al.,	2010
Propranolol	Basic	9.7	n. a.	River and lake surface–water filtered DOM; sediment-extracted DOM;	Humic acids; Fulvic acids; pony lake fulvic acid;	10	7	3.90/5.20	Peng et al.	2014
					Suwannee river fulvic acid;	10	7	4.70	Peng et al.	2014
Sarafloxacin	Zwitterion	n. a.	n. a.	Aldrich humic acids;	Humic acids;	1, 5, 12.5, 25, 50	3	4.77	Lützhøft et al..	2000
					Humic acids;	1, 5, 12.5, 25, 50	4	4.86	Lützhøft et al.	2000
					Humic acids;	1, 5, 12.5, 25, 50	5	5.19	Lützhøft et al.	2000
					Humic acids;	1, 5, 12.5, 25, 50	6	4.98	Lützhøft et al.	2000
					Humic acids;	1, 5, 12.5, 25, 50	7	4,74	Lützhøft et al.	2000
					Humic acids;	1, 5, 12.5, 25, 50	8	4.52	Lützhøft et al.	2000
Tetracycline	Zwitterion	3.3; 7.7; 7.9	n. a.	Reference standards	Leonardite humic acid	46.4	8	4.60	Ding et al.	2013
					Aldrich humic acid	79.4	8	3.27	Ding et al.	2013
Thiabendazole	Zwitterion	4.7, 12	2.47	Reference standards; synthesis;	Aldrich humic acid	5000-15000	7	2.58	Kim et al.	2010
					hydroxypropyl-b-cyclodextrin	20000	7	2.39	Kim et al.	2010
					POPC liposome	480-1703	7	n. a.	Kim et al.	2010
					sodium dodecyl sulfate	10000-25003	7	2.01	Kim et al.	2010

3

2.2.3 Hydrophobicity of dissolved organic matter and its impact on partitioning

The role of the different DOM fractions, namely hydrophobic or hydrophilic, and the sub-classes acidic, basic or neutral, on partitioning of pharmaceuticals depends on their chemical functionalities and degree of ionisation (Lützhøft et al. 2000; Michael-Kordatou et al. 2015). For example, hydrophobic DOM fractions dominate the distribution of the acidic naproxen and the neutral carbamazepine at low pH (4), whilst at more environmentally relevant pH (6.5 - 8), the hydrophilic DOM fractions were more influential (Maoz and Chefetz 2010). In fact, despite the predominance of the acidic fraction of the hydrophilic DOM, which is expected to show little affinity for the negatively-charged naproxen, there is evidence that the neutral and basic moieties play an important role in the binding of the neutral carbamazepine and the acidic ibuprofen (Hernandez-Ruiz et al. 2013). Notwithstanding, the contribution to binding of each fraction is determined by its relative abundance in DOM mixtures (Maoz and Chefetz 2010). The calculated values regarding sorption of pharmaceuticals to bulk DOM are based on experimentally discrete fractional sorption values, and differ from bulk experimental measurements (Maoz and Chefetz 2010). On this basis, it is hypothesised that DOM fractions interact with each other at the molecular level and do not behave as independent entities in the binding processes. Thus, studying DOM fractions as discrete entities may lead to incorrect estimates of pharmaceuticals partitioning to the bulk DOM (Maoz and Chefetz 2010).

2.3. Partitioning to colloids

The partitioning of pharmaceuticals to colloids is poorly understood, with little supporting research available. The available data show that pharmaceuticals partition to colloids to a greater degree than other sorbents (Fig 6) (Table 2). The sorption capacity

of colloids is determined by the type, influenced by its source and environmental compartment, such as freshwater, wastewater, or seawater. Such a variation can lead to large differences in partition coefficient values for the same pharmaceutical (Zhou et al., 2007). Examples include data for colloids from river water, treated effluent, and seawater showing a distribution coefficient variation of a factor of 6 - 12 for the synthetic oestrogen 17-α ethynylestradiol. In addition, despite a higher amount of colloidal fraction in the wastewater effluent, no major partitioning variation was observed between wastewater effluents and freshwater colloids, whilst higher K_{coc} values were observed for the lower concentrations of seawater colloids. This data confirms that the physical-chemical properties of the colloids have much more influence than their actual concentration on the distribution of pharmaceuticals (Zhou et al., 2007).

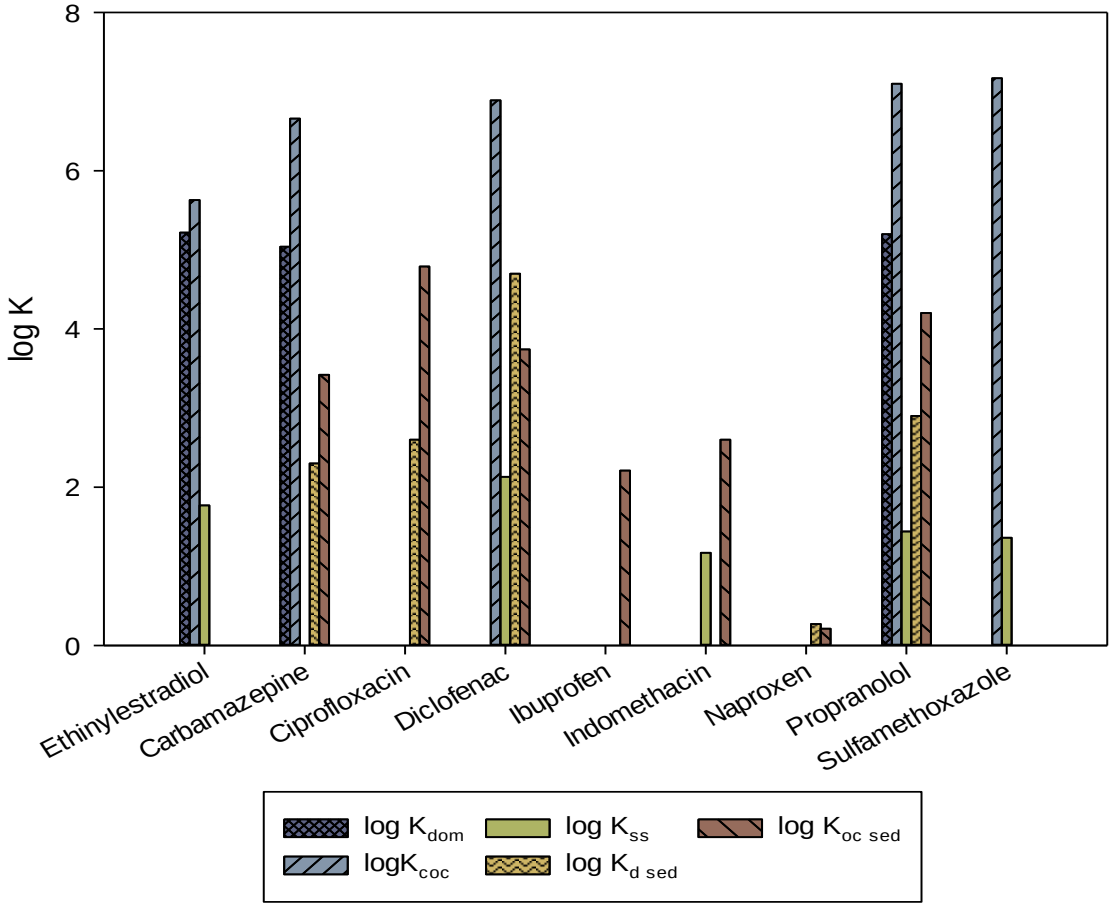

Fig 6. Comparison of pharmaceuticals partition coefficients for different sorbents, namely dissolved organic matter (log K_{dom}), colloids (log K_{coc}), suspended solids (log K_{ss}), and sediments -bulk (log $K_{d\ sed}$) and -normalized per organic matter fraction (log $K_{oc\ sed}$).

Table 2 Colloids partition coefficients (Log K_{coc}) for pharmaceuticals, source and size fraction, experimental concentration and pH. Legend: * metabolites; N.A. not available.

Compound	Type	pKa	$LogK_{ow}$	Source	Size fraction	Concentration (mg/L)	pH	Log K_{coc} [L/kg]	Reference	Year
17α-Ethynilestradiol	neutral	10.2	3.67	Biological wastewater treatment system	<30kD	6.0	7.1	5.2	Holbrook et al.	2004
				Biological wastewater treatment system	<30kD	5.3	7.1	3.0	Holbrook et al.	2004
				Biological wastewater treatment system	<30kD	4.9	7.1	5.2	Holbrook et al.	2004
				Biological wastewater treatment system	<30kD	5.1	7.1	4.5	Holbrook et al.	2004
				Biological wastewater treatment system	<100kD	5.9	7.1	4.7	Holbrook et al.	2004
				Biological wastewater treatment system	<100kD	5.4	7.1	4.5	Holbrook et al.	2004
				Biological wastewater treatment system	<0.22 µm	7.7	7.1	5.4	Holbrook et al.	2004
				Biological wastewater treatment system	<0.22 µm	7.5	7.1	4.9	Holbrook et al.	2004
				Biological wastewater treatment system	<0.22 µm	5.5	7.1	5.0	Holbrook et al.	2004
				Biological wastewater treatment system	<0.22 µm	7.1	7.1	5.3	Holbrook et al.	2004
				Biological wastewater treatment system	<1.5µm	8.9	7.1	4.8	Holbrook et al.	2004
				Biological wastewater treatment system	<1.5µm	7.7	7.1	5.0	Holbrook et al.	2004
				Biological wastewater treatment system	<1.5µm	6.2	7.1	4.9	Holbrook et al.	2004
				Biological wastewater treatment system	<1.5µm	7.8	7.1	5.2	Holbrook et al.	2004
				River water	between >1 kDa and <0.7 µm;	2.3	6.4	4.57	Zhou et al.	2007
				River water	between >1 kDa and <0.7 µm;	3	7.3	3.8	Zhou et al.	2007
				STWs effluents	between >1 kDa and <0.7 µm;	9.2	7.1	3.73	Zhou et al.	2007
				River water	between >1 kDa and <0.7 µm;	2.9	8.5	3.84	Zhou et al.	2007
				Sea water	between >1 kDa and <0.7 µm;	0.4	8	4.47	Zhou et al.	2007
				STWs effluents	between >1 kDa and <0.7 µm;	7.5	6.8	4.63	Zhou et al.	2007
Carbamazepine	neutral	13.94	2.93	River water; STWs effluents; groundwate;			n. a.	6.66	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	4.74	Maskaoui, Hibberd, & Zhou	2007
Diclofenac	acidic	4	4.51	River water; STWs effluents; groundwater;			n. a.	6.89	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	5.29	Maskaoui, Hibberd, & Zhou	2007
Indomethacin	acidic	3.96	4.27	River water; STWs effluents; groundwater;			n. a.	7.06	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	5.5	Maskaoui, Hibberd, & Zhou	2007
Mebeverine	basic	8.2	5.12	River water; STWs effluents; groundwater;			n. a.	n. a.	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	5.88	Maskaoui, Hibberd, & Zhou	2007

Meclofenamic acid	acidic	3.73	5	River water; STWs effluents; groundwater;			n. a.	n. a.	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	5.29	Maskaoui, Hibberd, & Zhou	2007
Propranolol	basic	9.7	1.2	River water; STWs effluents; groundwater;			n. a.	7.1	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	5.25	Maskaoui, Hibberd, & Zhou	2007
Sulfamethoxazole	basic	6.2	0.48	River water; STWs effluents; groundwater;			n. a.	7.17	Maskaoui and Zhou	2010
				River water	between >1 kDa and <0.7 µm;	0-30	n. a.	4.95	Maskaoui, Hibberd, & Zhou	2007
Tamoxifen	basic	8.87	6.3	River water; STWs effluents; groundwater;	n. a.	n. a.	n. a.	n. a.	Maskaoui and Zhou	2010
Thioridazine	basic	9.5	5.9	River water; STWs effluents; groundwater;			n. a.	n. a.	Maskaoui and Zhou	2010

Published data show no relationship between K_{oc} and K_{ow} for a series of pharmaceuticals (Yamamoto et al. 2003; Holbrook et al. 2004; Liu et al. 2005; Maskaoui et al. 2007), which has been related to mechanisms of sorption dictated chiefly by the charge on the pharmaceuticals rather than hydrophobicity(Yamamoto et al. 2003; Holbrook et al. 2004). Nevertheless, it should be noted that Maskaoui et al. (2007) showed a positive relationship between K_{coc} and K_{ow}, and postulated a role for hydrophobicity in controlling the partitioning processes of pharmaceuticals on colloids. However, the study did not present the experimental pH and the variability of the charge of the compounds studied. The pK_as suggest that most of the acidic and basic compounds would have been dissociated at environmental pH, which would strongly influence the relationship between K_{ow} and K_{coc}.

2.4. Partitioning to suspended solids & sediments

Preferential partitioning of some pharmaceuticals to suspended solids, and their absence in surface water solution in river catchments, highlights the significance of such sorbents (Ferreira Da Silva et al. 2011). Both the characteristics of the pharmaceutical and the suspended solids are important in determining observed behaviour; in this case, sorption was driven by the positively-charged functionality of the pharmaceutical (Ferreira Da Silva et al. 2011) (Table 3).

67 **Table 3** Suspended solids partition coefficients (Log K_d) and normalized to organic matter content (log Koc) for pharmaceuticals, source,
68 sorbent, experimental concentration and pH. Legend: * metabolites; N.A. not available.

Compound	Type	pKa	$LogK_{ow}$	Source	Sorbent	Concentration (mg/L)	pH	Log K_d [L/Kg]	Log K_{oc} [L/Kg]	Reference	Year
17α-Ethynilestradiol	neutral	10.2	3.67	Synthetic	Artificial alumina suspended particles coated with humic acid;	1	7.8	1.77	3.93	Ra et al.	2008
Amoxicillin	Zwitterion	2.8; 7.2	0.87	Synthetic wastewater	Suspended solids	160	3.5	0.41	n. a.	Githinji et al.	2011
							5.5	0.55	n. a.	Githinji et al.	2011
							6.6	0.64	n. a.	Githinji et al.	2011
							7.5	0.80	n. a.	Githinji et al.	2011
							8.5	1.08	n. a.	Githinji et al.	2011
Ciprofloxacin	Zwitterion	5.9; 8.9	0.28	Synthetic wastewater	Suspended solids	160	3.5	-0.17	n. a.	Githinji et al.	2011
							5.5	-0.05	n. a.	Githinji et al.	2011
							6.6	-0.07	n. a.	Githinji et al.	2011
							7.5	-0.21	n. a.	Githinji et al.	2011
							8.5	-0.36	n. a.	Githinji et al.	2011
Diclofenac	acidic	4	4.51	River water; STWs effluents;	Suspended solids	n. a.	n. a.	0.95	n. a.	Maskaoui and Zhou	2010
				Synthetic	Artificial alumina suspended particles coated with humic acid;	1	7.8	2.13	4.29	Ra et al.	2008
Gemfibrozil	acidic	4.5	4.7	Synthetic	Artificial alumina suspended particles coated with humic acid;	1	7.8	2.39	4.55	Ra et al.	2008
Ibuprofen	acidic	4.41	3.5	Synthetic wastewater	Suspended solids	n. a.	3.5	-2.77	n. a.	Paul et al.	2013
				Synthetic wastewater	Suspended solids	n. a.	6.5	-2.96	n. a.	Paul et al.	2013
				Synthetic	Alumina suspended particles coated with humic acid	1	7.8	1.59	3.76	Ra et al.	2008
Indomethacine	acidic	3.96	15	River water; STWs effluents;	Suspended solids	n. a.	n. a.	1.17	n. a.	Maskaoui and Zhou	2010
Mebeverine	neutral	8.2	5.12	River water; STWs effluents;	Suspended solids	n. a.	n. a.	n. a.	n. a.	Maskaoui and Zhou	2010
Meclofenamic acid	acidic	3.73	5	River water; STWs effluents;	Suspended solids	n. a.	n. a.	n. a.	n. a.	Maskaoui and Zhou	2010
Naproxen	acidic	4.2	3.18	Synthetic wastewater	Suspended solids	n. a.	3.5	-4.52	n. a.	Paul et al.	2013
						n. a.	6.5	-3.14	n. a.	Paul et al.	2013
Propranolol	basic	9.7	1.2	River water; STWs effluents;	Suspended solids	n. a.	n. a.	1.44	n. a.	Maskaoui and Zhou	2010
Sulfamethoxazole	basic	9.14; 13.84	0.48	River water; STWs effluents;	Suspended solids	n. a.	n. a.	1.36	n. a.	Maskaoui and Zhou	2010
Tamoxifen	basic	8.87	6.3	River water; STWs effluents;	Suspended solids	n. a.	n. a.	n. a.	n. a.	Maskaoui and Zhou	2010
Thioridazine	basic	9.5	5.9	River water; STWs effluents;	Suspended solids	n. a.	n. a.	n. a.	n. a.	Maskaoui and Zhou	2010

Tolfenamic acid	acidic	4.3	5.17	Synthetic	Artificial alumina suspended particles coated with humic acid;	1	7.8	2.79	4.95	Ra et al.	2008

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70 There are limited data on pharmaceutical sediment sorption, accumulation, and
71 formation of transformation products (Bu et al. 2013; Savci 2013) (Table 4). One study
72 reported concentrations 10 – 32 times higher in sediments than in water (Agunbiade and
73 Moodley 2015) with other studies confirming the importance of sediments as sorbents
74 (Stein et al. 2008; Yamamoto et al. 2009; Varga et al. 2010; Martínez-Hernández et al.
75 2014; Svahn and Bjorklund 2015; Li et al. 2015). For acidic pharmaceuticals, however,
76 the charge repulsion limits pharmaceutical - sediment interactions (Koumaki et al. 2016).

Table 4 Sediments partition coefficients (Log K_d) and normalized to organic matter content (log K_{oc}) for pharmaceuticals, source, and pH. Legend: * metabolites; N.A. not available.

Compound	Type	pKa	$logK_{ow}$	Source	pH	Log K_d (L/Kg)	Log K_{oc} (L/Kg)	Author	Year
10,11-dihydro-10,11-dihydroxycarbamazepine*	n. a.	n. a.	n. a.	River	7.7	-0.52	1.46	Loffler et al.	2005
				River	n. a.	-0.8-0.25	1.3-1.6	Stein et al.	2008
10,11-dihydrocarbamazepine*	n. a.	n. a.	n. a.	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
				River	n. a.	0.08-0.94	2.2-2.3	Stein et al.	2008
1-Naphthol+	neutral	9.6	2.7	Lake	6.8-8	n. a.	n. a.	Li et al.	2015
2-Hydroxyibuprofen+	acidic	4.6	2.4	Lake	6.8-9	n. a.	n. a.	Li et al.	2015
				River	7.7	n. a.	n. a.	Loffler et al.	2005
4-Amino-6-chloro-1,3-benzenedisulfonamide+	basic	9.2	-1	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
4-chlorobenzoic acid+	acidic	4.1	2.2	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
4'-Hydroxydiclofenac+	acidic	3.8	4	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Acebutolol	basic	9.2	1.71	Settleable particulate matter from wastewater treatment works effluents	n. a.	0.5-1.0	2.35-2.47	Lahti and Oikari	2011
				River		3.28	5.05	Lin et al.	2010
Acetaminophen	neutral	9.5	0.91	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River	n. a.	-0.3	0.75	Martínez-Hernández et al.	2014
				River	n. a.	0.41-1-0.44	4.11-2.43-5.4	Yamamoto et al.	2009
				River		0.7	2.47	Lin et al.	2010
Alprenolol	basic	n. a.	n. a.	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
Amitryptyline	basic	9.4	4.92	River	7	0.94-2.39	2.95-4.10	Al-Khazrajy and Boxall	2016
Atenolol	basic	9.6	0.16	Settleable particulate matter from wastewater treatment works effluents	n. a.	0.05-0.5	1.85-2.05	Lahti and Oikari	2011
				River	n. a.	0.9	-0.25	Martínez-Hernández et al.	2014
				River, lake	n. a.	n. a.	n. a.	Svahn and Bjorklund	2015
				River		0.11-0.9-0.72	3.23-2.92-2.5	Yamamoto et al.	2009
				River	7	0.34-1.31	1.93-2.7	Al-Khazrajy and Boxall	2016
Bendroflumethiazide	basic	n. a.	n. a.	River, lake		n. a.	n. a.	Svahn and Bjorklund	2015
Bezafibrate	acidic	3.6	4.25	Settleable particulate matter from wastewater treatment works effluents	n. a.	-0.5	1.41	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Bicalutamide	basic	12	2.7	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Bisoprolol hemifumarate	basic	9.5	1.87	Settleable particulate matter from wastewater treatment works effluents	n. a.	0.3-0.8	2.17-2.3	Lahti and Oikari	2011
Caffeine	basic	6.1	<0	River		1.25	-0.8	Martínez-Hernández et al.	2014
				River		2.4	4.16	Lin et al.	2010
Carbamazepine	neutral	13.9	2.45	Settleable particulate matter from wastewater treatment works effluents	n. a.	0.2-2.3	2.00-3.42	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River	7.7	0.11	1.92	Loffler et al.	2005
				River		-0.39	1.8	Martínez-Hernández et al.	2014

				River		0.23-1.09	2.4-2.5	Stein et al.	2008
				River, lake		n. a.	n. a.	Svahn and Bjorklund	2015
				River		-1.07-0.14-0.25	1.04-2.14-2	Yamamoto et al.	2009
				River		n. a.	2.6-3.7	Zhou and Broodbank	2014
Carbamazepine-10,11-epoxide+	neutral	16	2	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Carboxyibuprofen	acidic	4	2.8	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Chlorothiazide	basic	9.1	-0.44	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Chlortalidone	basic	8.6	1.6	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Cimetidine	basic	6.8	0.40	River	7	0.35-1.20	2.00-2.63	Al-Khazrajy and Boxall	2016
Ciprofloxacin	zwitterion	5.9-8.9	0.4	Settleable particulate matter from wastewater treatment works effluents	n. a.	2.6	4.79	Lahti and Oikari	2011
Citalopram	basic	9.6	1.39	Settleable particulate matter from wastewater treatment works effluents	n. a.	3.9-4.6	5.32-6.02	Lahti and Oikari	2011
Clofibric acid	acidic	3.4	2.9	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River	7.7	-0.52	1.41	Loffler et al.	2005
Codeine	basic	8.2	1.2	River		0.32-1.15	2.4-2.5	Stein et al.	2008
D3-ibuprofen	acidic	n. a.	n. a.	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
D5-fluoxetine	basic	n. a.	n. a.	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
Demeclocycline	basic	n. a.	n. a.	Setteable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
Diazepam	basic	3.4	2.85	River	7.7	0.48	2.28	Loffler et al.	2005
				River	n. a.	0.28-1.4	2.4-2.8	Stein et al.	2008
Diclofenac	acidic	4.2	4.51	Settleable particulate matter from wastewater treatment works effluents	n. a.	4.7	2.45-3.74	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River, lake		n. a.	n. a.	Svahn and Bjorklund	2015
				River	n. a.	1.58 to 2.71	n. a.	Zhou and Broodbank	2014
Dihydrocodeine*	basic	8.8	-1.5	River		0.15-0.81	2.3-2.2	Stein et al.	2008
Diltiazem	basic	8.06	2.8	River	7	1.34-3.00	2.90-4.12	Al-Khazrajy and Boxall	2016
Enrofloxacin	acidic	n. a.	n. a.	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
Fluconazole	basic	13	0.56	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Fluoxetine	basic	10.1	1.22	Settleable particulate matter from wastewater treatment works effluents	n. a.	2.9-4.1	4.09-5.49	Lahti and Oikari	2011
				River		1.25-2.7-3.63	4.38-4.7-5.4	Yamamoto et al.	2009
Furosemide	acidic	4.2	1.8	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River, lake		n. a.	n. a.	Svahn and Bjorklund	2015
Glimepiride	basic	4.3	3.1	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Hydrochlorothiazide	basic	9.1	-0.58	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Ibuprofen	acidic	4.9	3.97	Settleable particulate matter from wastewater treatment works effluents	n. a.	1.7	2.14-2.21	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River		7.7	n. a.	Loffler et al.	2005
				River		-1.03- -0.04- -0.52	2.07- 1.97 - 1.25	Yamamoto et al.	2009
Ifenprodil	basic	9.34, 9.99	n. a.	River		1.5 - 2.66 - 3.14	4.61 - 4.67 - 4.91	Yamamoto et al.	2009
Indomethacin	acidic	3.96	n. a.	River		-0.92 - 0.17 - 0.83	2.20 - 2.20 - 2.60	Yamamoto et al.	2009
Iopromide	basic	n. a.	-2.33	River		7.7	n. a.	Loffler et al.	2005
Ivermectin	neutral	n. a.	3.22	River		7.7	3.07	Loffler et al.	2005
Ketoprofen	acidic	4.5	3.12	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015

Mefenamic acid	acidic	3.73	2.42	River		1.30-0.74-1.08	4.43- -0.38-2.85	Yamamoto et al.	2009
				River	7	0.26-1.27	1.88-2.52	Al-Khazrajy and Boxall	2016
Metoprolol	basic	9.7	1.69	Settleable particulate matter from wastewater treatment works effluents	n. a.	0.2-0.9	2.22-2.24	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Metoprolol acid+	acidic	3.5	-1.2	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Morphine	basic	8	-0.1	River		0.5-1.33	12.6-2.7	Stein et al.	2008
N4-acetyl-sulfamethoxazole*	basic	n. a.	n. a.	River		-1.88- -0.15	0.24-1.2	Stein et al.	2008
Naproxen	acidic	4.2	3.18	Settleable particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River		0.27	0.21	Martínez-Hernández et al.	2014
Ofloxacin	zwitterion	6.0, 8.3	0.35	Suspended particulate matter from wastewater treatment works effluents	n. a.	2.5	4.64	Lahti and Oikari	2011
Oxazepam	basic	1.7	2.4	Suspended particulate matter from wastewater treatment works effluents	7.7	0.34	2.18	Loffler et al.	2005
				River		0.30-1.37	2.4-2.7	Stein et al.	2008
				River, lake		n. a.	n. a.	Svahn and Bjorklund	2015
Oxytetracycline	basic	3.3, 7.3, 9.1	-1.22	Suspended particulate matter from wastewater treatment works effluents	n. a.	2.5	4.64	Lahti and Oikari	2011
Paracetamol	basic	9.4	0.46	Suspended particulate matter from wastewater treatment works effluents	n. a.	n. a.	n. a.	Lahti and Oikari	2011
				Suspended particulate matter from wastewater treatment works effluents	7.7	n. a.	n. a.	Loffler et al.	2005
Propranolol	basic	9.7	2.6	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River sediment		0.34-2-2.20	3.46-4-3.97	Yamamoto et al.	2009
				River		2.43	4.2	Yu-Chen Lin et al.	2010
				River		1.89 to 2.9	3.11-3.95	Zhou and Broodbank	2014
Saluamine	acidic	4.4	0.66	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Sotalol	basic	9.6	0.24	Suspended particulate matter from wastewater treatment works effluents	n. a.	0.1-0.6	1.94-2.15	Lahti and Oikari	2011
				Lake	6.8-10	n. a.	n. a.	Li et al.	2015
Sulfamethoxazole	acidic	6.2	0.9	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				Aquifer		0.63	-0.17	Martínez-Hernández et al.	2014
				River		-0.7- -0.05	1.4-1.3	Stein et al.	2008
				River		1.41 to 2.67	n. a.	Zhou and Broodbank	2014
				River		0.75-1.44	2.19-2.8	Stein et al.	2008
Tramadol	basic	2.4	9.2	Lake	6.8-10	n. a.	n. a.	Li et al.	2015
				River		0.38-0.89	3.01-2.5	Stein et al.	2008
α-Hydroxymetoprolol+	basic	0.84	9.7	Lake		n. a.	n. a.	Li et al.	2015

2.4.1. *Influence of compound speciation*

The degree of pharmaceuticals ionisation influences partitioning on suspended solids (Table 3), with strong pH dependence for zwitterions, such as ciprofloxacin and amoxicillin, controlling partitioning to suspended solids in wastewater (Githinij et al. 2011). Acidic ibuprofen and naproxen were adsorbed in larger amounts at pH lower than their pK_a (4.4 and 4.2, respectively), where they were mainly in unionized form (Paul et al., 2014). In contrast, for zwitterions, an increase in K_d was observed at lower pH due to protonation of the amine group. As might be expected, higher K_d values were observed for amine-containing pharmaceuticals than for neutral or carboxylic compounds (Stein et al. 2008; Yamamoto et al. 2009; Martínez-Hernández et al. 2014; Svahn and Bjorklund 2015) (Table 4). For example, ibuprofen showed a significant increase in K_d as pH decreased from 7 to 4, the latter pH value being below the pK_a of the acidic compound (4.5), meaning that the neutral species dominated (Oh et al. 2016). Stein et al. (2008) showed that compounds with structures similar to carbamazepine and its metabolites, and some opiates and tranquilizers, had a similar distribution trend. Furthermore, the dominance of ionization over hydrophobicity as a sorption mechanism to suspended solids and sediments was confirmed by poor correlation of K_d and K_{ow} (Stein et al. 2008; Yamamoto et al. 2009).

2.4.2. *Sediment composition*

The importance of the sediment composition to sorption was demonstrated by a large variation in partition coefficients (log K_d) using field data from varying sampling locations (Zhou & Broodbank 2014). The organic carbon content of the sediment correlated with the degree of pharmaceutical sorption (Stein et al. 2008; Varga et al. 2010; Martínez-Hernández et al. 2014; Svahn and Bjorklund 2015), which is consistent with the large K_{oc} values reported (Table 4). Despite the important role played by the organic carbon

fraction, variability in cation exchange capacity and sediment texture can also influence sorption of pharmaceuticals (Al-Khazrajy and Boxall 2016; Le Guet et al. 2018). Furthermore, the molecular weight of pharmaceuticals was found to be positively correlated with K_{oc}, showing that the partitioning processes tended to favour relatively large molecules, similar to hydrophobic contaminants (Zhou and Broodbank 2014). Resuspension of sediment leads to a decrease in K_d (Zhou and Broodbank 2014). This is likely due the larger specific surface area of suspended solids compared with sediments, leading to a shift in equilibrium towards the more readily available exchange sites of the suspended solids.

2.4.3. Accumulation in sediments

The sorption of pharmaceuticals onto sediments and resuspendable suspended solids may lead to accumulation. pharmaceuticals contamination of the benthic environment in areas close to urban wastewater treatment works, with concentrations up to 200 ng g^{-1} dry weight, was reported (Lahti and Oikari 2011). Once in the sediment, pharmaceuticals may undergo transformation processes and release lower molecular weight, more soluble transformation products into the dissolved phase which, in turn, partition according to the physico-chemical properties of the newly-formed moieties. Thus, sediments have been considered a potential secondary source of pharmaceutical contamination, likely to occur over a wide area downstream of discharges and therefore should be recognized as part of the environmental risk caused by pharmaceuticals in the environment (Li et al. 2015).

2.4.5 Metabolite sorption

In addition to the parent compounds, sorption of metabolites is little understood, with only three studies having included metabolic products (Löffler et al. 2005; Stein et al.

2008; Lahti and Oikari 2011). Löffler et al. (2005) compared the sorption to sediments of 10 pharmaceuticals and metabolites, including diazepam and its metabolite oxazepam; ibuprofen and its metabolite 2-hydroxyibuprofen; carbamazepine and its metabolite 10, 11-dihydro-10,11-dihydroxycarbamazepine, metabolite and the active form of clofibrate of clofibric acid, iopromide, paracetamol, and ivermectin. Binding to sediments was ascribed by the authors as the main reason for rapid elimination of paracetamol from solution. Carbamazepine showed a moderate affinity for sediments, whilst the accumulation of 10,11-dihydro-10,11-dihydroxycarbamazepine was insignificant, most likely because of its high solubility and hydrophilicity (log K_{ow} = 0.13) (Miao et al. 2005). The lipid regulator, clofibric acid, showed a very low affinity for sediments at pH close to its pK_a of 7.7, suggesting low sorption under most environmental conditions. Due to its moderate hydrophobicity, oxazepam was rapidly and extensively partitioned to sediments (Löffler et al. 2005). The high hydrophobicity of ivermectin was reported as the main cause of rapid and extensive sorption to sediments. Ibuprofen partitioned to sediments only moderately, as did its metabolite 2-hydroxyibuprofen. In summary, sorption to sediments was elevated for ivermectin, diazepam, oxazepam, and carbamazepine with K_{oc} ranging from 1172 L kg^{-1} for ivermectin to 83 L kg^{-1} for carbamazepine (Löffler et al. 2005), consistent with their respective physico-chemical properties (Table 4).

2.5. Implication for environmental risk assessments

In the environmental risk assessment for `down-the-drain chemicals', such as pharmaceuticals, water is the main environmental compartment of concern (EMA 2006). As such, the distribution to DOM, colloids, suspended solids and sediments in surface fresh water are of importance in determining the environmental exposure of these contaminants. The sorption to freshwater sorbents is accounted for in the predicted

environmental concentration refinement of Tier B of the environmental risk assessment for pharmaceuticals by the calculation of a factor, as shown in Equation 1 (European Comission Joint Research Centre 2003; EMA 2006):

$$FACTOR = \left(1 + Kp_{susp} * SUSP_{water} * 10^{-6}\right) \quad (1)$$

Where Kp_{susp} is the distribution coefficient to suspended solids; and $SUSP_{water}$ the concentration of suspended solids.

However, this calculation considers sorption on suspended solids but not specifically on DOM and/or colloidal fractions. As DOM and colloidal matter are responsible for most sorption (Fig 6), their omission could lead to overestimation of exposure. Additionally, as evidenced from this study, the source and quality of the sorbent is a key factor in determining the partitioning extent of pharmaceuticals. This is particularly apparent when reference standards are used to assess the degree of sorption to DOM, and results in a high degree of uncertainty of the distribution capacity. These aspects should be addressed in site-specific risk assessment as they could profoundly affect the exposure estimate. The importance of the pH dissociation of the pharmaceuticals is also clearly demonstrable, which impacts significantly on the extent of sorption to freshwater sorbents.

3. Conclusions

As a general conclusion, there is a paucity of information on processes by which pharmaceuticals sorb to surfaces in aquatic environments. Nevertheless, reports show that the sorption of pharmaceuticals in the aquatic environment strongly depends on their chemical functionality and the sorbent properties, with basic compounds more readily adsorbed than neutral or acidic ones. Therefore, sorption increases at pH below pK_a for all functionalities. The comparison of the partition coefficients of the different

sorbents (Fig 6) shows a net predominance of sorption onto colloids, and the following general trend of sorption: colloids > DOM > sediments > suspended solids. The K_{ow} does not demonstrate a relationship with the distribution coefficients (K) of the polar and ionizable pharmaceuticals and the analyzed sorbents, which is most likely due to additional polar interactions between ionized pharmaceutical functional groups and the sorbent. Also, the adjustment of K to pH has not established a relationship between the adjusted partition coefficient (D) and K_{ow}.

With regard to DOM composition, humic substances generally show more affinity for pharmaceuticals than protein-like DOM, while a poor correlation was found between sorption of pharmaceuticals reference and to environmental DOM. Furthermore, it is important to note that the investigation of the role of different fractions of DOM in isolation does not represent an environmentally-realistic estimate of pharmaceutical sorption. Partitioning to colloids is significantly under-researched, with the limited available information suggesting they are a major physico-chemical variable controlling pharmaceutical partitioning in water. Concerning other identified sorbents, suspended solids interactions with pharmaceuticals show dependence on the degree of pharmaceutical ionization. Again, no relationship between K_{ow} and K_{dss} was demonstrated. Sediments can be considered both as a sink for pharmaceuticals and as a secondary source of pharmaceutical contamination in the form of transformation products. Differences in sediment K_d from separate studies are most likely influenced by differences in sediment composition, e.g. organic carbon content, grain size, clay fraction, cation exchange capacity, experimental conditions, and the concentration of pharmaceutical used, which can vary from mg L^{-1} in experimental conditions to ng L^{-1}.

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