

MCDUGALL, L., THOMSON, L., BRAND, S., WAGSTAFF, A., LAWTON, L.A. and PETRIE, B. 2021. Adsorption of a diverse range of pharmaceuticals to polyethylene microplastics in wastewater and their desorption in environmental matrices. *Science of the total environment* [online], 808, article 152071. Available from: <https://doi.org/10.1016/j.scitotenv.2021.152071>

Adsorption of a diverse range of pharmaceuticals to polyethylene microplastics in wastewater and their desorption in environmental matrices.

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2021

Supplementary materials have been appended to this accepted manuscript. They consist of one figure and three tables.

1 **Adsorption of a diverse range of pharmaceuticals to polyethylene microplastics in wastewater**
2 **and their desorption in environmental matrices**

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6 **Abstract**

7 It is proposed that microplastics discharged from wastewater treatment plants act as a vector of
8 pharmaceuticals. In this study, adsorption of pharmaceuticals to polyethylene microplastics was
9 investigated in municipal wastewater. Pharmaceuticals for study were selected to represent different
10 speciation (anionic, cationic, and neutral) and a range of pH dependant octanol-water distribution
11 coefficients ($\log D_{OW}$). Findings revealed adsorption favoured those in cationic form with the greatest
12 hydrophobicity (e.g., fluoxetine $\log D_{OW}$ 2.0 at pH 7.8). Adsorption of anionic pharmaceuticals was
13 restricted due to repulsion with the microplastic's negatively charged surface. Only atorvastatin had any
14 appreciable adsorption due to its comparatively high $\log D_{OW}$ value (2.9). Those pharmaceuticals
15 predominantly in neutral form (carbamazepine and ketamine) with $\log D_{OW}$ values ≥ 2.4 had similar
16 adsorption. Freundlich K_F values were 3400, 386, 284, 259 and 218 ($\text{mg kg}^{-1})(\text{mg L}^{-1})^{1/n}$ for fluoxetine,
17 propranolol, atorvastatin, ketamine, and carbamazepine, respectively. All pharmaceuticals with $\log D_{OW}$
18 values < 1.0 (atenolol, gliclazide, bezafibrate, and ifosfamide) did not adsorb to microplastics,
19 irrespective of their speciation. Changing composition of wastewater (pH, dilution with stormwater and
20 NaCl addition) within the range expected for municipal wastewater had limited influence on adsorption.
21 Pharmaceutical desorption from microplastics was assessed in river water and simulated gastric and
22 intestinal fluids. Solution pH was considered the most important factor for pharmaceutical desorption,
23 influencing both pharmaceutical speciation and microplastic surface charge. Greatest desorption was
24 observed for the cationic pharmaceuticals in gastric fluids due to a reduced surface charge of the
25 microplastics under low pH conditions. Up to 50 % desorption of fluoxetine occurred in gastric fluid at
26 37 °C. These findings show that pharmaceuticals adsorbed to microplastics are 'bioavailable'. However,

27 this is often overlooked as an exposure route to aquatic organisms because water samples are normally
28 pre-filtered prior to chemical analysis.

29 **Keywords:** water pollution; emerging contaminant; drug; sewage; microplastic; sorption

30 1. Introduction

31 Microplastics are plastic pieces smaller than 5 mm in all dimensions and those smaller than 1,000 nm
32 are termed nanoplastics (Gigault et al., 2018; Guo et al., 2019). Microplastics are ubiquitous in the
33 environment and can be present in the form they were manufactured (i.e., primary microplastics) or
34 from the breakdown of larger plastics (i.e., secondary microplastics) (Issac and Kandasubramanian,
35 2021). A common pathway for microplastics to enter the environment is the discharge of treated
36 effluents from wastewater treatment plants (WTPs) or combined sewer overflows (CSOs) following
37 heavy rainfall (Sun et al., 2019; Polanco et al., 2020). The most common polymer types of microplastics
38 found in wastewater include polyethylene, polyamide, and polyethylene terephthalate (Sun et al., 2019).
39 Treated effluents contain up to 447 particles L⁻¹ whilst untreated wastewater can contain up to >10,000
40 particles L⁻¹ (particles retained on a 10 µm steel filter) (Simon et al., 2018).

41 Research has found that other pollutants including persistent organic pollutants, pharmaceuticals,
42 pesticides, and personal care product ingredients can adsorb to the surface of microplastics (Wu et al.,
43 2016; Zhao et al., 2020; Mo et al., 2021). There are concerns that the refractory nature of microplastics
44 will result in the transport of these adsorbed pollutants for considerable distances from their source.
45 Furthermore, organisms can ingest microplastics resulting in their exposure to the adsorbed pollutants.
46 Microplastics have been found in the gastrointestinal tract or tissues of a variety of organisms including
47 birds, fish, macroinvertebrate, marine turtles, and seals (Duncan et al., 2019; Windsor et al., 2019; Zhu
48 et al., 2019; Wang et al., 2021; Weitzel et al., 2021).

49 Pharmaceuticals also enter the environment in wastewater and CSO discharges, with more than 200
50 individual pharmaceuticals previously detected in the environment (Hughes et al., 2013). Little research
51 has been undertaken on the adsorption of pharmaceuticals to microplastics in wastewater despite this
52 being a pathway for both pollutant types entering the environment. Wastewater is a heterogeneous

53 matrix containing comparatively high concentrations of other dissolved organic species. Previous
54 research has shown that other dissolved organics (e.g., humic acid) can enhance or reduce
55 pharmaceutical adsorption to microplastics (Xu et al., 2018a; Zhang et al., 2018). Other properties of
56 wastewater that vary (and can influence pharmaceutical adsorption) are pH, salinity, and temperature
57 (Elizalde-Velázquez et al., 2020; Lin et al., 2020; Puckowski et al., 2021).

58 Microplastics are typically negatively charged at the pH of municipal wastewater and electrostatic
59 interactions are important for understanding the adsorption of charged species to their surface (Tourinho
60 et al., 2019). Previous research found that cationic pharmaceuticals that are more hydrophobic in nature
61 adsorb to polyamide microplastics in wastewater under a range of conditions (Wagstaff et al., 2021).
62 However, pharmaceuticals are a diverse group of pollutants encompassing a broad range of
63 physicochemical properties. Research conducted in simple solutions (e.g., 0.01 M calcium chloride –
64 CaCl_2) have found that anti-inflammatories present in anionic form have little interaction with
65 microplastics at pH 6.9 (Elizalde-Velázquez et al., 2020). It has been concluded that the negative charge
66 of microplastics results in charge repulsion with the similarly charged pharmaceuticals. Further studies
67 have found that other anionic pharmaceuticals such as atorvastatin adsorb to microplastics (Liu et al.,
68 2020a), possibly due to its higher octanol-water partition coefficient. The pH dependent octanol-water
69 partition coefficient ($\log D_{ow}$) which accounts for hydrophobicity and speciation has been used to
70 indicate the likely environmental fate of pharmaceuticals (Zhang et al., 2012; Li et al., 2019). However,
71 there is a lack of studies which investigate the adsorption of a range of pharmaceuticals (cationic,
72 anionic, and neutral species) to microplastics under the same experimental conditions.

73 It is also important to consider the desorption of pharmaceuticals from microplastics in the variety of
74 environments they can enter. This is essential for those ionisable pharmaceuticals because the
75 gastrointestinal tract of exposed organisms has a range of pH environments. Other than pharmaceutical
76 speciation, the surface charge of microplastics change with pH (Xu et al., 2018b). It has been proposed
77 that changes to microplastic charge under low pH conditions of gastric fluids resulted in the release of
78 cationic pharmaceuticals from their surface (Wagstaff et al., 2021). However, only a few studies have
79 investigated the desorption of pharmaceuticals from microplastics under gastric or intestinal conditions

80 (Razanajatovo et al., 2018; Lin et al., 2020; Liu et al., 2020b). Further studies are now needed on
81 pharmaceuticals representing a range of properties to better understand their desorption from
82 microplastics in various environments.

83 The aim of this study was to investigate how a diverse range of pharmaceuticals interact with
84 microplastics in wastewater and to what extent they desorb in different environments. The objectives
85 of the study were to (i) investigate the adsorption of cationic, anionic, and neutral pharmaceuticals, with
86 a range of log D_{OW} values, to polyethylene microplastics in wastewater, (ii) determine the influence of
87 pH, salinity, stormwater dilution and temperature on their adsorption, and (iii) evaluate the desorption
88 of adsorbed pharmaceuticals in river water, gastric fluid, and intestinal fluid conditions. Polyethylene
89 microplastics were selected for study due to their prevalence in wastewater (Sun et al., 2019). The
90 cationic drugs atenolol, propranolol and fluoxetine, the anionic drugs gliclazide, bezafibrate and
91 atorvastatin, and the non-ionised drugs ifosfamide, carbamazepine and ketamine in wastewater (pH 7.8)
92 were investigated (Figure 1, Table S1). These pharmaceuticals represent a range of log D_{OW} values and
93 are often found in municipal wastewater (Petrie et al., 2016).

94 **2. Materials and methods**

95 **2.1. Materials**

96 Pharmaceutical reference standards of atenolol, atorvastatin calcium trihydrate, bezafibrate,
97 carbamazepine, codeine (as internal standard), fluoxetine hydrochloride, gliclazide, ifosfamide,
98 ketamine hydrochloride and propranolol hydrochloride were purchased from Sigma Aldrich
99 (Gillingham, UK). Sodium azide (NaN_3), sodium chloride (NaCl), sodium taurocholate (98 %), bovine
100 serum albumin (>98 %) and pepsin A ($\geq 500 \text{ U mg}^{-1}$) were also obtained from Sigma Aldrich. Methanol,
101 ammonium formate and formic acid of high-performance liquid chromatography (HPLC) grade as well
102 as GF/F glass fibre filter papers, 4 mm PVDF 0.45 μm syringe filters, hydrochloric acid (HCl) and
103 sodium hydroxide (NaOH) were obtained from Fisher Scientific (Loughborough, UK). Ultrapure water
104 was 18.2 $\text{M}\Omega \text{ cm}^{-1}$ quality. Ultra-high molecular weight polyethylene microplastics (mean size 150 μm)
105 were purchased from Goodfellow Cambridge Limited (Huntingdon, UK; Table 1). Municipal
106 wastewater (50 L) was collected from a septic tank in North-East Scotland during May 2021 and frozen

107 at -20 °C. The wastewater did not contain detectable levels of any of the studied pharmaceuticals.
108 Stormwater (road runoff, 5 L) and river water (5 L) was also collected and frozen at -20 °C.

109 2.2. Adsorption experiments

110 Wastewater was defrosted overnight, filtered through GF/F filters and 0.2 g L⁻¹ sodium azide added to
111 limit microbial activity. Wastewater volumes of 20 mL had 10 mg of polyethylene microplastic (0.5 g
112 L⁻¹) added in 20 mL borosilicate bottles with screw top caps lined with aluminium. These were kept in
113 the dark at 20 °C and mixed using a flask shaker (Cole-Palmer, Staffordshire, UK) at 500 oscillations
114 (osc) min⁻¹. A pharmaceutical concentration of 0.5 mg L⁻¹ was used to establish uptake kinetics and
115 equilibrium time. Samples were collected at 0, 0.5, 1, 2, 3, 4, 6 and 24 hours. The uptake kinetics were
116 fitted using the pseudo-second order model (eq. 1):

$$117 \frac{t}{q_e} = \frac{1}{K_2 q_e^2} + \frac{1}{q_e} t \quad (1)$$

118 q_e (mg kg⁻¹) is the adsorbed pharmaceutical concentration, t (hours) is the mixing time and K_2 (kg mg⁻¹
119 h⁻¹) is the equilibrium rate constant.

120 Pharmaceutical concentrations of 0.1, 0.2, 0.3, 0.4, 0.5, 0.75, 1 and 2 mg L⁻¹ in wastewater were used
121 to determine adsorption isotherms. The linear (eq. 2), Freundlich (eq. 3) and Langmuir isotherms (eq.
122 4) were used to model the data:

$$123 q_e = K_d C_e \quad (2)$$

$$124 q_e = K_F C_e^{1/n} \quad (3)$$

$$125 q_e = \frac{q_{max} K_L C_e}{1 + K_L C_e} \quad (4)$$

126 C_e (mg L⁻¹) is the remaining pharmaceutical concentrations in wastewater, K_d (L kg⁻¹) is the distribution
127 coefficient between the microplastic and wastewater, K_F [(mg kg⁻¹)(mg L⁻¹)^{1/n}] and n are the Freundlich
128 constants. Q_{max} (mg kg⁻¹) is the estimated maximum adsorption capacity and K_L (L mg⁻¹) is the Langmuir
129 constant.

130 Pharmaceutical adsorption was investigated at pH 3, 6, 7, 8 and 11. To investigate the influence of
131 stormwater dilution on pharmaceutical adsorption varying compositions of wastewater:stormwater
132 (100:0, 75:25, 50:50, 25:75 and 0:100) were prepared. Salinities of 0, 2.5, 5, 7.5 and 10 g L⁻¹ NaCl in
133 50:50 wastewater:stormwater were also investigated. To assess the influence of temperature on
134 pharmaceutical adsorption, experiments were conducted in wastewater at 5 °C and 20 °C. All samples
135 were collected following 6 hours of mixing. Equivalent experiments without microplastic were utilised
136 to evaluate any pharmaceutical losses to glassware for all experiments. All experiments were performed
137 in triplicate. Samples were passed through 0.45 µm PVDF filters and spiked with 1 mg L⁻¹ of the
138 appropriate internal standard and analysed within 24 hours (see Table S2, Wagstaff et al., 2021).

139 **2.3. Desorption experiments**

140 Adsorption of pharmaceuticals at 2 mg L⁻¹ was undertaken to ensure adequate adsorbed concentrations
141 for desorption studies. Following adsorption, samples were filtered through GF/F filters and the retained
142 microplastics transferred to a flask containing 20 mL desorption medium. The desorption media
143 investigated were filtered river water (20 °C), simulated intestinal fluids (20 °C and 37 °C) and
144 simulated gastric fluids (20 °C and 37 °C). Intestinal fluids and gastric fluids were prepared as described
145 in Lui et al (2020). Intestinal fluid comprised of 5 g L⁻¹ bovine serum albumin and 10 mM sodium
146 taurocholate in 100 mM NaCl (pH 7) and gastric fluid 3.2 g L⁻¹ pepsin A in 100 mM NaCl (pH 2) (Liu
147 et al., 2020). Samples were prepared in triplicate and collected at 1, 2, 3, 4 and 24 hours. They were
148 prepared for analysis as described in Section 2.2.

149 **2.4. Analytical methods**

150 Analysis was performed with an Agilent 1260 Infinity Series HPLC coupled to a 6420 triple quadrupole
151 mass spectrometer. Separation was performed on a 100 x 2.1 mm Kinetex 5 µm C18 column
152 (Phenomenex, Cheshire, UK) using a gradient elution at 0.3 mL min⁻¹ of water and methanol, with both
153 containing 10 mM ammonium formate and 0.1 % formic acid (see Table S3 for details). The column
154 temperature was 25 °C and the injection volume was 2 µL. All samples were analysed against a
155 calibration curve prepared in wastewater ranging from 0.01 to 2.5 mg L⁻¹, with 1 mg L⁻¹ internal
156 standard. Preparing the calibration curve in matrix compensated for any matrix effects. Details of MRM

157 transitions are outlined (Table S2). Wastewater spiked with known concentrations of pharmaceuticals
158 were used as quality control samples. Procedural blanks (non-spiked wastewater) were also prepared
159 and analysed. Zeta potential measurements were made using a Zetasizer Nano ZS (Malvern Panalytical,
160 Malvern, UK).

161 **2.5. Statistical analysis**

162 The effect of pH, dilution of wastewater with stormwater, and NaCl addition on pharmaceutical
163 adsorption to polyethylene microplastics were analysed using one-way ANOVA followed by Tukey's
164 multiple comparison tests. The effect of temperature was analysed by unpaired t-tests followed by
165 Welch's correction. Differences in desorption at different exposure times was assessed by one-way
166 ANOVA. The statistical analysis was performed using Prism v.9.0.1 (GraphPad Software, USA). A *p*-
167 value of <0.05 was considered significant.

168 **3. Results and discussion**

169 **3.1. Adsorption of pharmaceuticals to polyethylene microplastics in wastewater**

170 The adsorption of pharmaceuticals to polyethylene microplastics was assessed during 24 hours of
171 mixing. A flask shaker was used to ensure complete mixing of the polyethylene microplastic in
172 wastewater. The common approach of mixing microplastics (including polyethylene) in water for
173 adsorption studies is to use an orbital or reciprocal shaker (e.g., see Razanajatovo et al., 2018; Xu et al.,
174 2018b; Elizalde-Velázquez et al., 2020). However, it was found that the polyethylene floated, with half
175 of its surface not exposed to the wastewater, irrespective of mixing speed or the length of time mixing
176 took place. Therefore, more vigorous shaking was achieved using a flask shaker at 500 osc min⁻¹. This
177 ensured adequate mixing to replicate the turbulent nature of wastewater as it is transported through
178 pipes and sewers to the WTP.

179 Five of the studied pharmaceuticals had sufficient adsorption such that a measurable difference was
180 possible between the wastewater which did not have microplastic added (control), and the wastewater
181 with microplastics removed by filtration following mixing. These were propranolol, fluoxetine,
182 atorvastatin, carbamazepine, and ketamine. Fluoxetine had the greatest adsorption (~ 360 mg kg⁻¹),

183 followed by propranolol ($\sim 190 \text{ mg kg}^{-1}$) and then atorvastatin, carbamazepine, and ketamine (all ~ 70 -
184 80 mg kg^{-1}). Their adsorption fitted the pseudo-second order kinetic model with coefficient of
185 determination (r^2) values ≥ 0.997 (Table 2). As can be observed in Figure 2 and Table 2, both the
186 calculated and experimental values of q_e compare well. Previous research has found that the adsorption
187 of pharmaceuticals to polyethylene microplastics fits the pseudo-second order model (Razanajatovo et
188 al., 2018; Xu et al., 2018b). The remaining pharmaceuticals atenolol, gliclazide, bezafibrate and
189 ifosfamide had no appreciable adsorption to the polyethylene microplastics. Adsorption equilibrium for
190 all pharmaceuticals was achieved within the first few hours of mixing (Figure 2). Therefore, for future
191 studies all samples were collected following 6 hours mixing to ensure equilibrium was reached. Typical
192 sewer residence times of wastewater during dry weather conditions are up to 24 hours (Petrie et al.,
193 2019).

194 The equilibrium time was comparatively faster than the previous study with polyamide microplastics
195 in wastewater despite studying some of the same pharmaceuticals (e.g., propranolol and fluoxetine)
196 (Wagstaff et al., 2021). However, this is due to using a higher pharmaceutical to microplastic ratio in
197 the present study which results in faster equilibration (Atugoda et al., 2021). The microplastic
198 concentration in wastewater was 0.5 g L^{-1} instead of 2.5 g L^{-1} used previously (Wagstaff et al., 2021).
199 Short adsorption equilibration times have also been found for ciprofloxacin (3 hours) and triclosan (0.5
200 hours) to polyethylene microplastics (Atugoda et al., 2020; Chen et al., 2021).

201 The data fitted to the linear isotherm across the pharmaceutical concentration range studied (0.1 - 2 mg
202 L^{-1}) with r^2 values ranging from 0.800 for carbamazepine to 0.998 for fluoxetine (Table 2). The
203 determined partition coefficients (K_d) values were 440 , 3350 , 227 , 182 and 216 L kg^{-1} for propranolol,
204 fluoxetine, atorvastatin, carbamazepine, and ketamine, respectively. The adsorption data was also fitted
205 to the Freundlich and Langmuir isotherms with r^2 values in the range 0.821 - 0.997 (Table 2, Figure S1).
206 The pharmaceuticals had similar or greater r^2 values when fitted to the Freundlich isotherm compared
207 to the Langmuir isotherm (Table 2). Fitting to the Freundlich isotherm indicates heterogeneous
208 multilayer adsorption to the polyethylene surface (Guo et al., 2019). The Freundlich isotherm has been

209 used numerous times to model the adsorption of pharmaceuticals to microplastics (Razanajatovo et al.,
210 2018; Zhang et al., 2018; Guo et al., 2019).

211 The pharmaceuticals studied were selected to represent a range of speciation (positively charged,
212 negatively charged and non-ionised or neutral form) and log D_{OW} values at the pH of the studied
213 wastewater. It should be noted that at pH 7.8 ketamine was present in both non-ionised (81 %) and
214 cationic form (19 %) while all other drugs were present as a single species (≥ 99 %) (Figure 1). The
215 adsorption of pharmaceuticals to polyethylene microplastics followed fluoxetine > propranolol >
216 atorvastatin > ketamine > carbamazepine (Table 2). Adsorption favoured those in cationic form (e.g.,
217 fluoxetine and propranolol). This is unsurprising considering polyethylene holds a negative surface
218 charge at pH 7.8 (Table 1). Several studies report that electrostatic interactions are important for the
219 adsorption of pharmaceuticals to microplastics (Seidensticker et al., 2018; Tourinho et al., 2019;
220 Puckowski et al., 2021). However, despite being positively charged in wastewater no appreciable
221 adsorption of atenolol occurred. Atenolol has a low log D_{OW} value (-1.7) compared to fluoxetine (2.0)
222 and propranolol (1.8) at pH 7.8 demonstrating that charge alone cannot be used to describe their
223 adsorption to polyethylene microplastics, and hydrophobicity is also important for cationic
224 pharmaceuticals. Hydrophobic interactions are the attraction of non-polar or slightly polar molecules to
225 the non-polar microplastic surface (Tourinho et al., 2019). Polyethylene is considered non-polar due to
226 the C-C and C-H bonds of the repeating monomer (Table 1).

227 There was no adsorption of the anionic pharmaceuticals gliclazide (log D_{OW} -1.1) and bezafibrate (log
228 D_{OW} 0.0) due to charge repulsion with the microplastic and their low hydrophobicity. On the other hand,
229 the negative charge of atorvastatin was compensated for by its greater hydrophobicity (log D_{OW} 2.9).
230 However, atorvastatin adsorption was significantly lower than both propranolol and fluoxetine despite
231 its higher log D_{OW} value (Table 2). Both ketamine (log D_{OW} 3.0) and carbamazepine (log D_{OW} 2.4) also
232 had substantially lower adsorption than fluoxetine and propranolol, but similar adsorption (and log D_{OW}
233 values) to atorvastatin. Whereas ifosfamide had a log D_{OW} value of 0.9 but no appreciable adsorption.
234 Puckowski et al (2021) previously showed greater adsorption of propranolol over anionic and neutral
235 pharmaceuticals with similar log D_{OW} values. Therefore, pharmaceutical speciation is essential for

236 understanding their adsorption to polyethylene microplastics, but this needs consideration with their
237 hydrophobicity.

238 **3.2. Influence of wastewater characteristics to pharmaceutical adsorption**

239 The influence of pH, stormwater dilution, NaCl addition and temperature on pharmaceutical adsorption
240 to polyethylene microplastics in wastewater was investigated. Adsorption was studied at pH 3, 6, 7, 8
241 and 11 to encompass typical wastewater pH values (6-8) and acidic and basic conditions (pH 3 and 11)
242 to better understand the dominant adsorption interactions. Propranolol and fluoxetine showed a similar
243 trend whereby greatest adsorption occurred at pH 7 and 8 (Figure 3). Reduced adsorption was observed
244 at pH 3 despite both pharmaceuticals still being in the cationic form (Figure 1). At pH 3 the microplastic
245 had reduced surface charge as demonstrated by the zeta potential measurements (Table 1), resulting in
246 reduced interactions with these pharmaceuticals. These results agree with previous studies on
247 propranolol (Puckowski et al., 2021; Wagstaff et al., 2021) and fluoxetine (Wagstaff et al., 2021).
248 However, at pH 11 their adsorption was lower in comparison to pH 7 and 8 (Figure 3). At pH 11
249 propranolol and fluoxetine are present in non-ionised form demonstrating the significance of charged
250 interactions on the adsorption of these drugs to the polyethylene surface. Interestingly, previous
251 research found augmented adsorption of propranolol to polyamide in wastewater at pH 11 (Wagstaff et
252 al., 2021), and to polyethylene in 0.01 M CaCl₂ at pH 12 (Puckowski et al., 2021). This suggests that
253 the interactions between pharmaceuticals and microplastics are different between polymer types, but
254 also with the same microplastic polymer in different background solutions.

255 On the other hand, atorvastatin adsorption increased when present in the non-ionic form. The K_d value
256 was 1354 L kg⁻¹ at pH 3 and between 158 and 368 L kg⁻¹ when in anionic form at pH values 6, 7, 8 and
257 11 (Figure 3). This is like data obtained on naproxen, ibuprofen and diclofenac which have similar
258 speciation at different pH values (Elizalde-Velázquez et al., 2020). It should be noted that when present
259 in the non-ionised form atorvastatin has the greatest log D_{OW} value of all the studied pharmaceuticals
260 (Figure 1). Furthermore, both gliclazide (216 L kg⁻¹) and bezafibrate (267 L kg⁻¹) adsorbed to the
261 polyethylene microplastics at pH 3 and not under any other condition studied. Wastewater pH did not
262 affect carbamazepine adsorption which is in neutral form across the pH range studied (Figure 1, Figure

263 3). This agrees with a previous study which showed little influence of solution pH on carbamazepine
264 adsorption to polyethylene microplastics (Seidensticker et al., 2018). Ketamine showed a similar trend
265 to propranolol and fluoxetine with respect to speciation and adsorption. Greatest adsorption was
266 observed at pH 6 when present in the cationic form (Figure 1, Figure 3). Lower adsorption at pH 3 was
267 due to the reduced surface charge of the microplastics and low adsorption at pH values ≥ 7 when present
268 in non-ionic form (Figure 3).

269 Pharmaceutical adsorption to polyethylene microplastics was investigated in wastewater diluted with
270 increasing amounts of stormwater. Dilution had little influence on adsorption with only fluoxetine
271 showing a significant reduction (ANOVA, $p < 0.05$) between undiluted wastewater and 100 %
272 stormwater (Figure 3). Previous research has found that bulk organics such as humic acid can act as a
273 bridge for cations and zwitterions to adsorb to some microplastics (Zhang et al., 2018). Indeed, greater
274 adsorption of cationic pharmaceuticals to polyamide microplastics was found in undiluted wastewater
275 compared to diluted wastewater (Wagstaff et al., 2021). Previous studies report that due to the
276 hydrophilic properties of humic acid it has little interaction with polyethylene (Wu et al., 2016).
277 However, humic acid has been found to adsorb to polyamide (Zhang and Bai, 2002). Polyamide has
278 polar functional groups within its structure which could facilitate interactions with hydrophilic organics
279 such as humic acid. Nevertheless, pharmaceutical adsorption to polyethylene microplastics in
280 wastewater was largely unaffected by stormwater dilution expected during storm events that lead to
281 CSO discharges.

282 Salt applied to roads during winter months is mainly comprised of NaCl (>97 %) (Prosser et al., 2017).
283 These enter wastewater from road run-off into combined sewers. Run-off following de-icing has been
284 found to contain $\sim 1 \text{ g L}^{-1} \text{ Na}^+$ (Barbier et al., 2018), although concentrations could be considerably
285 higher. Therefore, the influence of salinity (up to $10 \text{ g L}^{-1} \text{ NaCl}$) on pharmaceutical adsorption in
286 wastewater was investigated. Only fluoxetine demonstrated reduced adsorption in the presence of
287 additional NaCl (Figure 3). The Na^+ ion can result in a charge shielding effect on the microplastic
288 surface (Lu et al., 2018). If this was the case it may be expected that increased adsorption of atorvastatin
289 may be observed due to reduced repulsion between the anionic species of the pharmaceutical and the

290 microplastic surface. However, no trend in the data between atorvastatin adsorption and NaCl
291 concentration was observed (Figure 3). Previous research showed that NaCl addition has no influence
292 on the adsorption of sulfamethoxazole present as the anionic species (Xu et al., 2018b), however other
293 research has shown that the influence of NaCl on sulfamethoxazole adsorption is less clear (Guo et al.,
294 2019). The addition of NaCl did not affect carbamazepine or ketamine adsorption to polyethylene
295 (Figure 3). Similar observations have been made for carbamazepine up to a NaCl concentration of 3.5
296 g L⁻¹ (Wu et al., 2016).

297 The influence of wastewater temperature on pharmaceutical adsorption was assessed at 5 °C and 20 °C.
298 The data suggested a species dependent effect on adsorption whereby only the cationic pharmaceuticals
299 showed a significant change. Both propranolol and fluoxetine had significantly reduced adsorption in
300 wastewater at 5 °C (Figure 3). This has also been observed for the adsorption of propranolol, fluoxetine,
301 and amitriptyline to polyamide microplastics (Wagstaff et al., 2021). Tetracycline adsorption to
302 polyamide microplastics has also been found to increase with increasing temperature (Lin et al., 2020).
303 Endothermic adsorption processes see an increase in adsorption with increased temperature (Xu et al.,
304 2021). However, it should be noted that wastewater temperatures are only likely to reach 5 °C in
305 treatment processes with long retention times (e.g., lagoons) during winter months (Delatolla et al.,
306 2019).

307 **3.3. Pharmaceutical desorption from polyethylene microplastics in river water, gastric fluid** 308 **and intestinal fluids**

309 The desorption of propranolol, fluoxetine, atorvastatin, carbamazepine, and ketamine was investigated
310 in river water (pH 7.4), gastric fluid at 20 °C and 37 °C (pH 2) and intestinal fluid at 20 °C and 37 °C
311 (pH 7). Gastric and intestinal fluids were maintained at both 20 °C and 37 °C to represent temperatures
312 of cold- and warm-blooded organisms (Liu et al., 2020; Wagstaff et al., 2021). Desorption occurred
313 rapidly for all pharmaceuticals in the studied matrices (Figure 4). There was little difference in
314 desorption between 1, 2, 3, 4 and 24 hours exposure in any of the matrices. Only atorvastatin in river
315 water and gastric fluid, and fluoxetine in intestinal fluid at 20 °C showed significant differences between

316 different exposure times. Liu et al. (2020) previously reported a fast desorption phase for atorvastatin
317 and amlodipine from polystyrene microplastics.

318 Propranolol had 11-12 % desorption in river water (Figure 4). This was increased to 23-26 % in gastric
319 fluid and 21-23 % in intestinal fluid at 20 °C (Figure 4). Previous research has found similar desorption
320 of propranolol from polyamide microplastics in river water and gastric fluid at 20 °C (Wagstaff et al.,
321 2021). Razanajatovo et al. (2018) reported ~8 % desorption from polyethylene microplastics in
322 intestinal fluid. Enhanced desorption was observed in both gastric and intestinal fluids at warm-blooded
323 over cold-blooded organism temperatures. At 37 °C the desorption was 32-33 % in gastric fluid and 24-
324 29 % in intestinal fluids (Figure 4). Higher desorption of pharmaceuticals at 37 °C over 18 °C has been
325 observed in gastric and intestinal fluids (Liu et al., 2020), and in intestinal fluid at 37 °C over 27 °C
326 (Lin et al., 2020). However, >50 % desorption for propranolol from polyamide microplastics has been
327 observed in gastric fluids at 37 °C previously (Wagstaff et al., 2021).

328 Fluoxetine showed a similar trend to propranolol albeit greater desorption was observed across the
329 matrices studied; 9-13 % in river water, 34-40 % in gastric fluid at 20 °C and 46-50 % at 37 °C, and 20-
330 28 % in intestinal fluid at 20 °C and 19-21 % at 37 °C (Figure 4). The desorption observed in river
331 water and gastric fluid is like equivalent studies using polyamide microplastics (Wagstaff et al., 2021).
332 In contrast, desorption of atorvastatin from polyethylene followed intestinal fluid > river water > gastric
333 fluid (Figure 4). Furthermore, there was no appreciable difference in desorption between cold- and
334 warm-blooded temperatures of gastric and intestinal fluids. Desorption was ~20 % in intestinal fluids.
335 Previous research has found >50 % desorption is possible from polystyrene microplastics in intestinal
336 fluids (Liu et al., 2020). On the other hand, little difference in desorption was observed for
337 carbamazepine or ketamine between the different matrices (and temperatures) studied. Carbamazepine
338 desorption was in the range 13-19 % and ketamine 9-11 % for all individual time points and desorption
339 matrices.

340 Our findings suggest that the pH of the matrix has the greatest influence on desorption of
341 pharmaceuticals from polyethylene microplastics. Enhanced desorption of the cationic pharmaceuticals
342 reflects their reduced adsorption in the low pH adsorption studies due to a lower surface charge of the

343 microplastic at this pH and less electrostatic attraction (Figure 3; Table 2). Atorvastatin also showed
344 increased adsorption (Figure 3) and reduced desorption at low pH (Figure 4). In this case it is the change
345 in pharmaceutical speciation from anionic to non-ionised form that is considered to account for the low
346 desorption observed in gastric fluid (shifting from predominantly electrostatic attraction to stronger
347 hydrophobic interactions). Furthermore, as pH did not influence adsorption of carbamazepine and
348 ketamine between low pH conditions and pH 7 (Figure 3), there was no change to their desorption
349 between matrices with different pH. Gastric and intestinal components (pepsin, bovine serum albumin
350 and sodium taurocholate) may also contribute to desorption for some pharmaceuticals. Liu et al. (2020)
351 reported they can increase desorption of atorvastatin and amlodipine (cationic speciation at neutral pH)
352 from polystyrene through increased solubilisation of the drugs and competition for adsorption sites on
353 the microplastic. However, in our study lower desorption of atorvastatin was observed in gastric fluid
354 compared to river water, and there was no difference in desorption for carbamazepine or ketamine
355 between river water and gastric or intestinal fluids.

356 **3.4. Environmental significance**

357 The study revealed that a diverse range of pharmaceuticals can adsorb to polyethylene microplastics in
358 wastewater. Changing wastewater characteristics (pH, dilution with stormwater, salinity) within
359 expected ranges of municipal wastewater have little effect on pharmaceutical adsorption. Only
360 fluoxetine adsorption was significantly impacted by NaCl addition to wastewater, and ketamine
361 adsorption in the pH range 6-8 (Figure 3). However, adsorption of ionised pharmaceuticals will be
362 significantly influenced by changes to pH out with expected values of municipal wastewater (pH 6-8).
363 Those pharmaceuticals present as cationic species had the greatest adsorption to polyethylene
364 microplastics. Exposure of microplastics to river water revealed pharmaceuticals had low desorption in
365 the range 10-20 % (Figure 4). This suggests that most of the adsorbed pharmaceutical concentration can
366 remain on the microplastic once discharged into the environment. Considerable desorption was
367 observed for the cationic pharmaceuticals in gastric fluid with up to 50 % desorption observed for
368 fluoxetine at 37 °C (Figure 3). This is significant as it demonstrates that microplastic bound
369 pharmaceuticals are 'bioavailable' if consumed and enter the gastrointestinal tract. However, a common

370 approach of assessing the risk posed by pharmaceuticals in wastewater effluents or river water is to
371 compare predicted no effect concentrations (PNECs) or environmental quality standards with pre-
372 filtered environmental samples (e.g., Singh and Suthar, 2021; An et al., 2022; Ofrydopoulou et al.,
373 2022). Therefore, the contribution of particle bound pharmaceuticals released in wastewater effluents
374 are not considered.

375 As a ‘worst-case scenario’, the amount of fluoxetine in river water associated with polyethylene
376 microplastics from WTP effluents ($Fluoxetine_{MP}$, mg L⁻¹) was estimated using eq. 5.

$$377 \quad Fluoxetine_{MP} = \frac{MP_{eff} \times q_e}{DF} \times \frac{(100 - des)}{100} \quad (5)$$

378 Where MP_{eff} is the concentration of polyethylene microplastics in wastewater effluent (kg L⁻¹). This is
379 the median concentration of microplastics in effluent taken from Ngo et al. (2019) and assuming 50 %
380 of the microplastic concentration is polyethylene (2.5 x 10⁻⁷ kg L⁻¹), q_e is the adsorbed fluoxetine
381 concentration calculated using eq. 2 (4.4 mg kg⁻¹). This was calculated using the highest reported
382 fluoxetine concentration in influent wastewater (Bean et al., 2017, 1.3 x 10⁻³ mg L⁻¹) and the K_d value
383 from Table 2. DF is a default dilution factor of 10 for wastewater effluents in river water (European
384 Medicines Agency, 2006), and des is the average desorption in river water from Figure 4 (10 %). Using
385 this information, the concentration of fluoxetine adsorbed to polyethylene microplastics in the mixing
386 zone of the river is equivalent to 1.0 x 10⁻⁷ mg L⁻¹. This represents 5 % and 4 % of the fluoxetine PNEC
387 compiled by Pereira et al. (2020) for invertebrate and fish, respectively. This seems small compared to
388 the PNEC, however this is just one exposure route of bioavailable fluoxetine for organisms in the
389 environment. There will also be exposure to free or ‘dissolved’ fluoxetine as well as fluoxetine adsorbed
390 to other microplastics and particulates discharged from WTPs. Although the approach taken here has
391 considerable uncertainties, it demonstrates that pharmaceuticals adsorbed to microplastics needs to be
392 considered as an exposure route to organisms in the environment, and not accounting for these adsorbed
393 pollutants can underestimate exposure and risk.

394 4. Conclusion

395 A range of pharmaceuticals including those in cationic, anionic, and neutral form adsorb to polyethylene
396 microplastics in wastewater. Both pharmaceutical speciation and hydrophobicity are important for
397 adsorption with those cationic and more hydrophobic in nature having the greatest adsorption. Changing
398 composition of wastewater (pH, dilution with stormwater and NaCl addition) typically expected for
399 municipal wastewater had little effect to pharmaceutical adsorption. However, changes to pH out with
400 the typical range of municipal wastewater (pH 6-8) had a significant influence on those ionisable
401 pharmaceuticals. Adsorbed pharmaceuticals had low desorption ($\leq 19\%$) in river water. Up to 50 %
402 desorption of fluoxetine was found in gastric fluids at 37 °C. Findings suggest that despite low amounts
403 of pharmaceuticals entering the environment adsorbed to polyethylene microplastics they are still an
404 important exposure route for aquatic organisms. Further research is needed to understand the risks posed
405 by the cocktail of pharmaceuticals adsorbed to the surface of microplastics and released into the
406 environment from WTPs.

407 **Acknowledgements**

408 Support by the Royal Society of Edinburgh is greatly appreciated. AW is grateful to the Carnegie
409 Trust for the Universities of Scotland for the award of a vacation scholarship.

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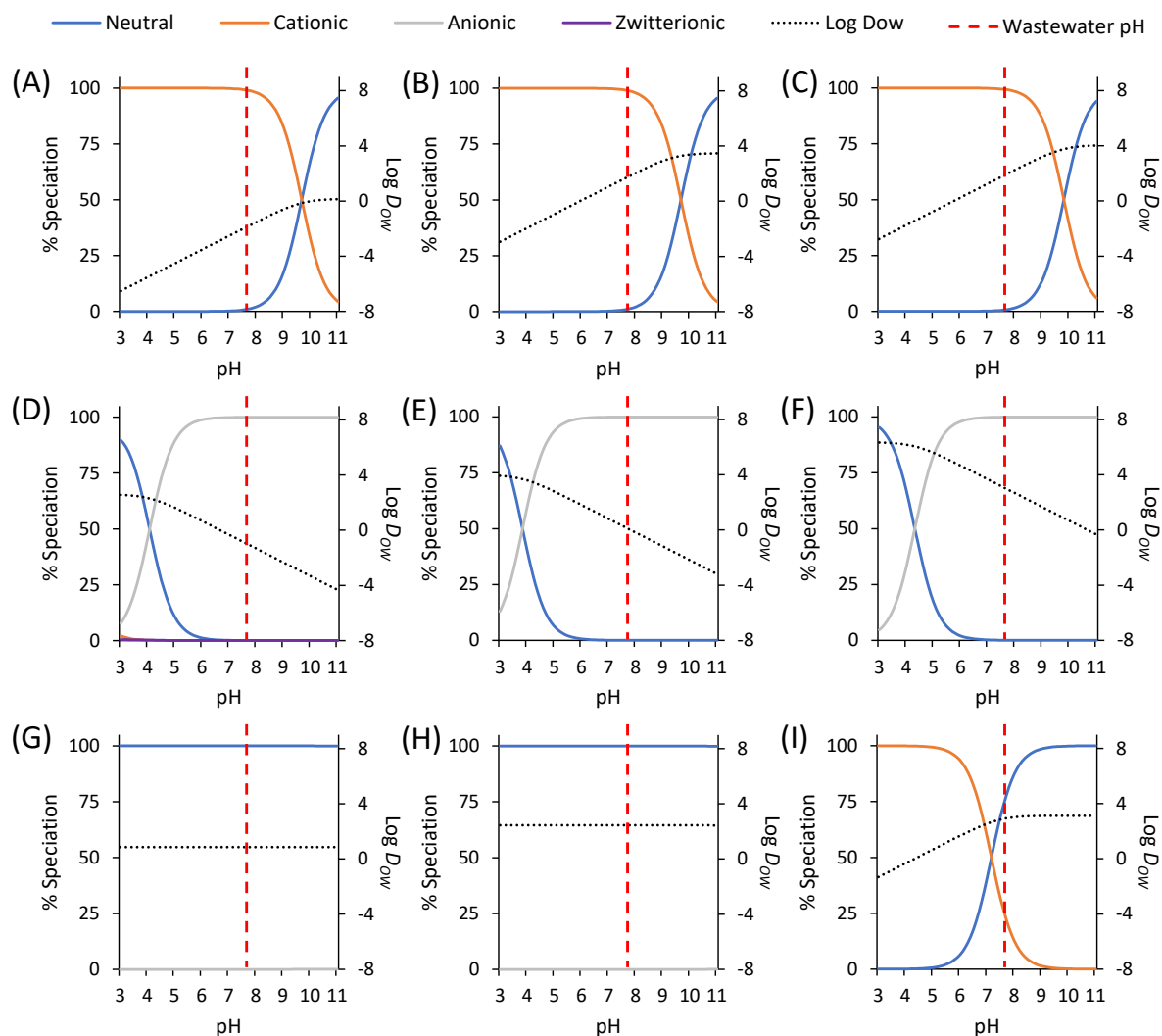
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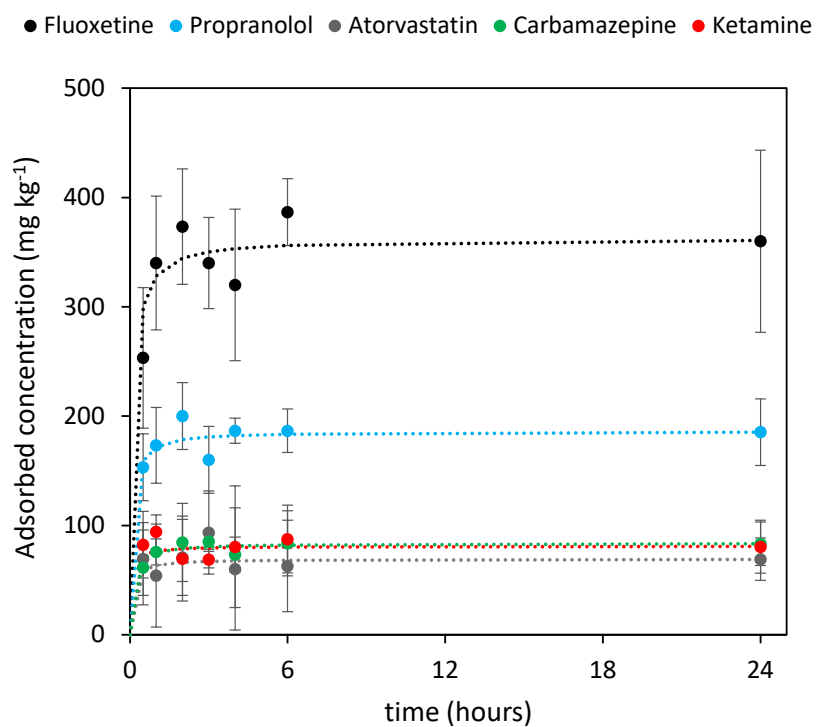
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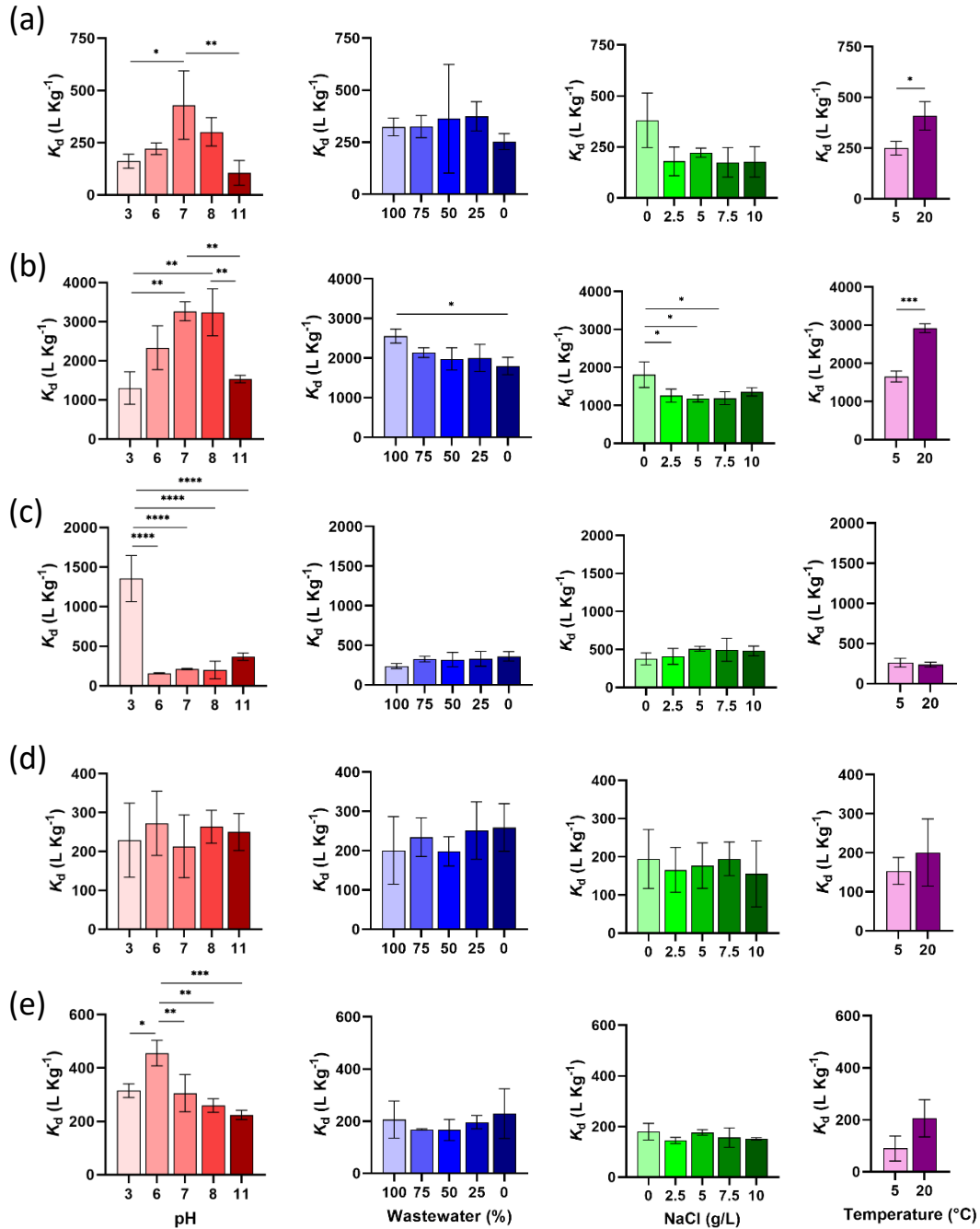


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 562 Figure 1. Speciation of studied pharmaceuticals at different pH values. Pharmaceuticals are grouped
 563 based on their dominant species at the pH of the studied wastewater (7.8) - cationic (A, atenolol; B,
 564 propranolol; C, fluoxetine), anionic (D, gliclazide; E, bezafibrate; F, atorvastatin) and neutral or
 565 predominantly non-ionised (G, ifosfamide; H, carbamazepine; I, ketamine). The pH dependant
 566 octanol-water partition coefficient ($\log D_{OW}$) is presented on the secondary axis. Data obtained from
 567 ChemAxon, 2021 and PubChem, 2021. The $\log D_{OW} = \log K_{OW}$ for ifosfamide and carbamazepine.
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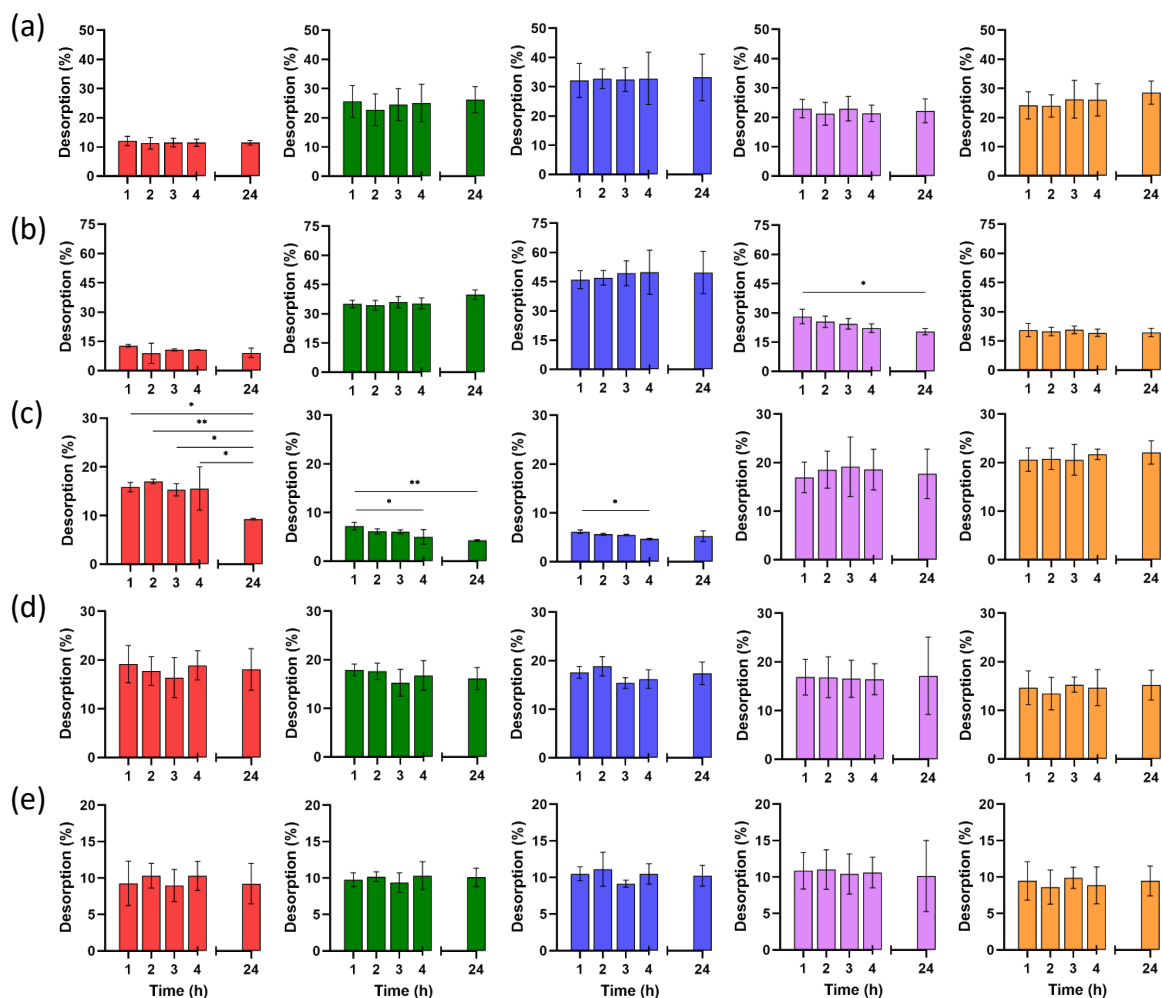
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Figure 2. Adsorbed concentration of fluoxetine, propranolol, ketamine, atorvastatin, and carbamazepine to polyethylene microplastics in wastewater over 24 hours. The dashed line represents the data fitted to the pseudo-second order model.



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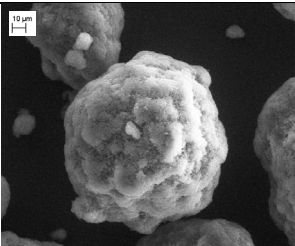
Figure 3. Influence of pH (red bars), wastewater-stormwater composition (blue bars), addition of NaCl (green bars) and temperature (lilac bars) on pharmaceutical adsorption to polyethylene microplastics. The different pharmaceuticals studied were propranolol (a), fluoxetine (b), atorvastatin (c), carbamazepine (d) and ketamine (e). The y-axis scale is different for each pharmaceutical. The asterisks represent statistical significance whereby * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$ based on one-way ANOVA for pH, wastewater % and NaCl and on unpaired t -tests for wastewater temperature.



589 Figure 4. Desorption of pharmaceuticals from polyethylene microplastics in river water at 20 °C (red
 590 bars), gastric fluid at 20 °C (green bars), gastric fluid at 37 °C (blue bars), intestinal fluid at 20 °C
 591 (lilac bars) and intestinal fluids at 37 °C (orange bars). The different pharmaceuticals studied were
 592 propranolol (a), fluoxetine (b), atorvastatin (c), carbamazepine (d) and ketamine (e). The y-axis scale
 593 is different for each pharmaceutical. The asterisks represent statistical significance whereby * $p < 0.05$
 594 and ** $p < 0.01$ based on one-way ANOVA.

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601 Table 1. Properties of the ultra-high molecular weight polyethylene microplastics

Monomer	Molecular weight (g mol ⁻¹) ^a	Mean size (μm) ^a	Density (g cm ⁻³) ^a	Zeta potential (mV)	SEM image ^b
$\left(\begin{array}{cc} \text{H} & \text{H} \\ & \\ \text{---C} & \text{---C} \\ & \\ \text{H} & \text{H} \end{array} \right)_n$	~5 x 10 ⁶	150	0.94	-10.5 (pH 3)	
				-19.5 (pH 6)	
				-21.1 (pH 7)	
				-26.8 (pH 8)	
				-28.9 (pH 11)	

602 ^aAs detailed by the manufacturer ^b1,000 x magnification

603 Key: SEM, scanning electron microscopy

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606 Table 2. Kinetics and isotherm data for pharmaceuticals and polyethylene microplastics in wastewater

Model	Type	Parameter	Pharmaceutical drug				
			Propranolol	Fluoxetine	Atorvastatin	Carbamazepine	Ketamine
Kinetics	Pseudo-second order	q_e (mg kg ⁻¹)	186	362	69.1	83.7	80.9
		K_2 (kg mg ⁻¹ h ⁻¹)	6.34×10^{-2}	2.67×10^{-2}	0.165	9.60×10^{-2}	0.226
		r^2	0.999	0.999	0.997	0.999	0.999
Isotherm	Linear	K_d (L kg ⁻¹)	440	3.35×10^3	227	182	216
		r^2	0.978	0.998	0.921	0.800	0.877
		Freundlich	K_F [(mg kg ⁻¹)(mg L ⁻¹) ^{1/n}]	386	3.40×10^3	284	218
	Langmuir	n	0.793	0.937	1.44	1.38	1.32
		r^2	0.984	0.997	0.964	0.821	0.900
		q_{max} (mg kg ⁻¹)	1.52×10^5	4.70×10^5	1.29×10^5	631	922
	Langmuir	K_L (L mg ⁻¹)	2.55×10^{-3}	6.82×10^{-3}	2.15×10^{-3}	0.549	0.412
		r^2	0.955	0.994	0.843	0.822	0.907

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Electronic supplementary material

Adsorption of a diverse range of pharmaceuticals to polyethylene microplastics in wastewater and their desorption in environmental matrices

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The electronic supplementary information contains one figure and three tables showing adsorption isotherms, properties of studied pharmaceuticals, the mobile phase gradient and MS/MS parameters.

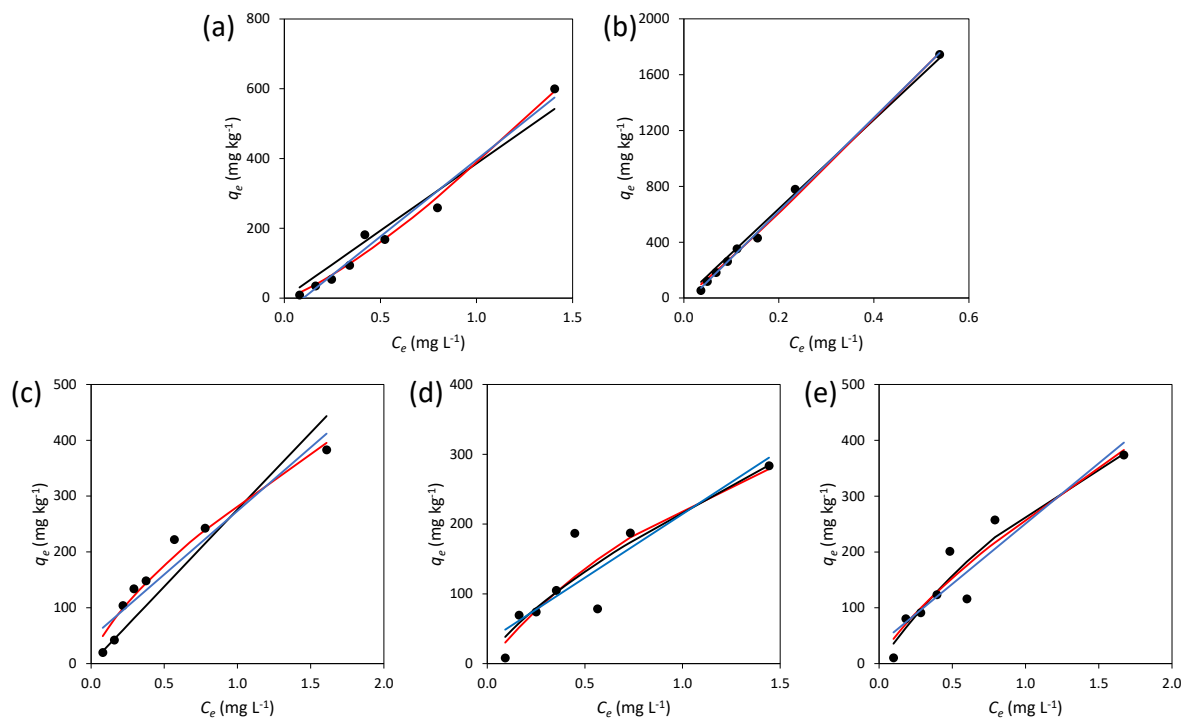


Figure S1. Linear (blue), Langmuir (black), Freundlich (red) isotherms of propranolol (a), fluoxetine (b), atorvastatin (c), carbamazepine (d), and ketamine (e) adsorption to polyethylene microplastics in wastewater. Circles show the experimental data.

Table S1. Properties of the studied pharmaceuticals (ChemAxon, 2021; Pubchem 2021)

Dominant species at pH 7.6	Pharmaceutical	Therapeutic group	Molecular mass (g mol⁻¹)	p<i>K</i>_a	Log <i>K</i>_{ow}^a
Cationic	Atenolol	Betablocker	266.34	9.67	0.16
	Propranolol	Betablocker	259.34	9.42	3.48
	Fluoxetine	Antidepressant	309.33	9.80	4.05
Anionic	Gliclazide	Antidiabetes	323.41	4.07	2.60
	Bezafibrate	Lipid-lowering	361.82	3.83	3.99
	Atorvastatin	Lipid-lowering	558.64	4.31	6.36
Neutral	Ifosfamide	Chemotherapeutic	261.08	14.64	0.86
	Carbamazepine	Anti-epilepsy	236.27	15.96	2.45
	Ketamine	Anaesthetic	237.73	7.45	3.12

^aoctanol-water partition coefficient

Table S2. MS/MS parameters of all pharmaceuticals and internal standards determined in positive ionisation mode

Pharmaceutical	R_t (minutes)	Precursor (m/z)	Fragmentor (V)	Product 1 (m/z)	CE (eV)	Product 2 (m/z)	CE (eV)	Internal standard
Atenolol	3.4	266.9	110	189.9	20	145.0	30	Codeine
Propranolol	10.6	259.9	110	182.9	10	115.9	10	Carbamazepine
Fluoxetine	12.4	309.8	90	147.7	2	44.0	10	Carbamazepine
Gliclazide	12.5	324.0	100	110.0	20	91.0	40	Carbamazepine
Bezafibrate	13.1	362.0	100	316.1	10	139.0	30	Carbamazepine
Atorvastatin	13.8	559.2	100	440.1	20	250.0	40	Carbamazepine
Ifosfamide	9.5	260.8	100	92.0	30	153.9	20	Propranolol
Carbamazepine	11.5	236.8	130	193.9	20	178.9	40	Propranolol
Ketamine	7.9	238.1	100	125.0	10	220.0	30	Propranolol
Codeine ^a	4.8	300.0	100	214.9	20	-	-	-

Key: R_t , retention time; CE, collision energy

^aInternal standard only

Table S3. Mobile phase gradient used for the determination of pharmaceuticals

Time (minutes)	10 mM ammonium formate and 0.1 % formic acid in water (%)	10 mM ammonium formate and 0.1 % formic acid in methanol (%)
0.0	90	10
0.5	90	10
10.0	20	80
14.5	20	80
14.6	90	10
21.0	90	10

References

ChemAxon, 2021. Calculator Plugins were used for structure property prediction and calculation, Marvin 20.16.0, <http://www.chemaxon.com> Accessed 15/02/21.

Pubchem, Maryland, USA, 2021. National Institutes of Health <https://pubchem.ncbi.nlm.nih.gov>. Accessed 05/01/21.