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Development and application of the diffusive gradients in thin-films technique for measuring psychiatric pharmaceuticals in natural waters

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ABSTRACT

Psychiatric pharmaceuticals are widely distributed in the aquatic environment and have attracted recent attention due to their potential for environmental effects. A robust and reliable *in situ* passive sampling approach, the diffusive gradients in thin-films (DGT) technique, is developed here to measure 14 psychiatric pharmaceuticals. A new binding material, mixed-mode cation exchange resin (Poly-Sery MCX, 40μm, CNW, Germany), was used for the first time in DGT and compared to XAD and HLB. Reliable elution efficiencies of the pharmaceuticals from the binding gels were obtained in methanol/ammonia and diffusion coefficients for all the compounds were determined. The influence of diffusive layer thickness (0.515−2.015 mm), deployment time (3−168 h), and important environmental conditions – pH (3.02−9.45), ionic strength (0.0001−0.5 M) and dissolved organic matter (0−20 mg L^{-1}) - were evaluated. The capacity of XAD, HLB and MCX gels for binding all the test pharmaceuticals was ~335 μg per disc, meaning that DGT could theoretically be deployed for over 30 months, if there are no competitive effects or confounding factors. The uptake kinetics of psychiatric pharmaceuticals onto MCX gel were much faster than to XAD and HLB gels in the first hour. DGT measured concentrations of test pharmaceuticals at two sample points in a river (over 6 days) were comparable to those obtained by grab sampling. This study demonstrates the accuracy and reliability of DGT for measuring psychiatric pharmaceuticals across the wide range of freshwater conditions found in the natural environment.

INTRODUCTION

Psychiatric pharmaceuticals are now widely used in many modern societies to treat mental health conditions.[1] For example, in the United Kingdom, the prescription of fluoxetine (FHY) increased 19% between 2011-2016.[2] The number of people using antidepressants in Denmark increased from ~250k to ~380k from 2000 to 2014,[3] while in the United States, the total quantities of benzodiazepines used to treat insomnia trebled from 1.1 to 3.6 kilogram per 100,000 adults between 1996 and 2013.[4] Despite passing through wastewater treatment processes, psychiatric pharmaceuticals have become ubiquitous in receiving waters.[5-8] For example, diazepam concentrations in many European river waters have been reported in the several 10s ng L^{-1} range.[6,8,9] Average FHY concentrations in effluents from China mental hospitals were ~21 ng L^{-1} in a Chinese study,[10] and ~55 ng L^{-1} in influents and effluents in Italy.[11] Oxazepam concentrations were as high as 942 ng L^{-1} in sewage influents of some psychiatric hospitals in China.[12] Studies have reported negative effects of psychiatric pharmaceuticals on aquatic animals[13, 14] and human health,[15] by directly acting on the central nervous system and disrupting neuro-endocrine signaling.[7]

Precise measurement and monitoring are pre-requisites to better understand the fate and biogeochemical behavior of these compounds and to further assess their potential effect on ecosystems and human health. So far studies have mainly simply been conducted by spot grab sampling. Although grab sampling is the most commonly used method for organic contaminants monitoring in waters, it usually needs large

volume water samples for solid phase extraction (SPE), with potential problems of sample storage, shipment, pretreatment and labour costs, while grab sampling only provides a snapshot of target analyte concentrations at the given sampling time, rather than giving more meaningful time weighted average concentrations (TWA).[16]

As a power-free sampling method, passive sampling techniques are now increasingly being used to pre-concentrate the analytes of interest onto binding agents in situ.[17] Passive sampling techniques are considered by many to be more convenient, economical, and time-saving and to give more meaningful TWA results on the biologically available fraction of contaminants in waters. The most frequently used passive sampling devices for organic contaminants in waters have been semi-permeable membrane devices (SPMDs)[18, 19] and polar organic chemical integrative sampler (POCIS).[17] However, their measurements are influenced by the hydrodynamic (flow) conditions of the water, due to the influence of the diffusion boundary layer (DBL) on sampling rate. They require calibration to correct for the effect of the DBL. In contrast, the diffusive gradients in thin films (DGT) technique contains a well-defined diffusive layer which controls the uptake of analytes and reduces the effect of the DBL on the measurement.[20] DGT provides *in situ* sampling of trace chemicals in water without field calibration.[21] The principle of DGT is based on Fick's first law of diffusion. The concentration of analyte measured by DGT, C_{DGT}, is expressed as eq 1.

$$C_{\mathrm{DGT}} = \frac{\mathrm{M}\Delta\mathrm{g}}{\mathrm{DA}t} \qquad (1)$$

M is the measured mass of target analyte accumulated in the binding layer, Δg

expresses the thickness of the diffusive layer, D is the diffusion coefficient of the target analyte in the diffusive layer, t is the exposure time, and A is the window area of the DGT device.

Invented in the 1990s for work on heavy metals and nutrients, DGT has been developed over recent years for many classes of trace organic contaminants, including antibiotics,[22] pesticides,[23] herbicides,[24] bisphenols (BPs),[25] perfluoroalkyl substances (PFASs),[26] organophosphorus flame retardants (OPFRs),[16] and pharmaceuticals and personal care products (PPCPs).[27] Most studies have used HLB and XAD18 as the binding material for DGT devices.

The aim of this study is to develop a new DGT method for measuring psychiatric pharmaceuticals in waters and apply it to natural aquatic systems. Anew binding gel was prepared using a strong cation exchange resin, MCX, because psychiatric pharmaceuticals are mostly in the cationic form in natural waters.[10] The two commonly used resins, XAD18 and HLB, were also used in test experiments to find the most suitable binding gels for 14 of the most commonly used psychiatric pharmaceuticals.

Diffusion coefficients required to calculate environmental concentrations of the psychiatric pharmaceuticals from a DGT deployment were determined and reported for the first time. To ensure DGT can be used to sample these compounds across the full range of natural environments, the effects of environmental conditions (pH, ionic strength, and dissolved organic matter), diffusive gel thickness, deployment time, storage time and competition between different psychiatric pharmaceuticals on DGT

103 performances were systemically tested. Finally, the three different types of DGT
104 devices with different binding gels were deployed in the field and compared with grab
105 sampling, to check its reliability and robustness for measurement and monitoring of
106 psychiatric pharmaceuticals.

107 EXPERIMENTAL SECTION

108 **Chemicals and Reagents.** Antidepressants and hypnagogues are two large classes
109 of commonly used psychiatric pharmaceuticals. The following antidepressants were
110 selected for study from 4 types of the most commonly used classes, namely: tricyclic
111 antidepressants (TCAs); selective serotonin reuptake inhibitor (SSRIs);
112 noradrenalin-dopamine re-uptake inhibitor (NDRI) and norepinephrine and specific
113 5-hydroxytryptamine antidepressant (NaSSA).[28,29] Target compounds were:
114 fluoxetine hydrochloride (FHY), risperidone (RIS), caffeine (CAF), clomipramine
115 (CLO), fluvoxamine maleate (FMA), mirtazapine (MIR), perphenazine (PER),
116 amitriptyline (AMI), and bupropion hydrochloride (BUP). Benzodiazepines are more
117 common hypnagogues in clinical application than barbiturates,[30] so the following
118 target analytes were selected: estazolam (EST), diazepam (DIA), temazepam (TEM),
119 alprazolam (ALP), and oxazepam (OXA). All psychiatric pharmaceutical standards
120 were purchased from Merck (Germany). $^{13}C_3$-caffeine was used as an internal
121 standard and purchased from Cambridge Isotope Laboratories (CIL, USA).
122 Physicochemical properties of all target psychiatric pharmaceuticals are described in
123 the Supporting Information (Table S1). HPLC grade methanol and ammonia water
124 were purchased from Merck (Germany) and CMW (Germany), respectively.

DGT Preparation. A standard piston DGT device consists of a 0.5-mm-thick agarose-based binding gel, a 0.75-mm-thick agarose-based diffusive gel, and a filter membrane, which are sandwiched by an ABS-based plastic molding (DGT Research Ltd., UK). Preparation of the agarose diffusive gel has been described previously.[16] Adsorption of target psychiatric pharmaceuticals on DGT-related materials, such as agarose diffusive gels, filter membranes, and DGT plastic molding, was tested. Agarose diffusive gel discs and four types of filter membranes (all with 2.5 cm diameter) [GH polypro (GHP, 0.114 mm thick, Pall, USA), Nuclepore track-etched polycarbonate membrane (PC, 0.015 mm thick, Whatman, USA), polyethersulfone (PES, 0.14 mm thick, Pall, USA), and polytetrafluoroethylene (PTFE, 0.14 mm thick, Pall, USA)], were separately immersed in 10 mL mixed solution of the 14 target chemicals, each at a concentration of 20 μg L^{-1}, while a set of DGT plastic moldings was immersed in 200 mL solution of the same composition. All solutions were shaken horizontally for 24 h. The adsorbed mass of the target chemicals was calculated by the difference of solution concentrations before and after the adsorption experiment.

The binding gels were prepared using three types of resins, Amberlite™ macroporous adsorbents resin XAD18 (XAD18, 75 μm particle size, Rohm and Hass Co., USA), hydrophilic lipophilic balanced resin (HLB, collected from Oasis-HLB SPE cartridges, 60 μm particle size, Waters, UK), and Poly-Sery MCX (40 μm particle size, MCX, CNW, Germany), and tested for their performance. Before gel making, these resins were activated with methyl alcohol for 0.5 h and then thoroughly washed using Milli-Q (18.2 MΩ cm, Millipore, USA) water. The procedure for

147 making the binding gels was: 2 g (wet weight after pre-treatment) of resins was added
148 into 10 mL of 2 % agarose solution and then heated to boiling together. This agarose
149 solution was pipetted between two preheated glass plates (~70 °C) separated by 0.5
150 mm thick PTFE spacer and left to cool down to room temperature. Once the gel was
151 set, open the glass plates with care and then cut into discs with a diameter of 2.5 cm.

152 **Uptake Kinetics and Elution Efficiencies of Binding Gels.** XAD18, HLB or
153 MCX based binding gel discs were immersed separately in 40 mL of 100 μg L^{-1}
154 psychiatric pharmaceutical solutions containing 0.01 M NaCl, and shaken
155 horizontally for up to 24 h. At different times from 0.5 min to 24 h, 50 μL samples
156 were taken from the solutions for analysis. The masses of target psychiatric
157 pharmaceuticals bound by the gel discs at different time were calculated by the
158 difference between the initial concentration and the concentration at collection of
159 solution subsamples at different time intervals. A control solution having the same
160 compositions without gel immersion was set to test the potential adsorption of target
161 chemicals onto the container wall.

162 Eq. S1 indicates that a stable elution efficiency is important to calculate the
163 adsorbed masses of analytes and hence assess the DGT-measured concentrations.
164 Therefore, to determine elution efficiencies of target psychiatric pharmaceuticals,
165 XAD (containing XAD18 resin), HLB (containing HLB resin), and MCX (containing
166 MCX resin) binding gel discs were immersed separately in 10 mL of pharmaceuticals
167 solutions at 10, 20 and 100 μg L^{-1} (containing 0.01 M NaCl), respectively, and shaken
168 for 24 h at 25 °C. Psychiatric pharmaceuticals adsorbed by the binding gel discs were

eluted using 10 mL of methanol containing 0.1%, 5%, or 10% (volume ratio) ammonia solution (the initial concentration of ammonia solution is 13 mol L^{-1}), respectively, in an ultrasonic bath for 3 hours. After filtration using 0.22 μm pore size PTFE filter membranes, the elution solutions were analyzed using UPLC−MS/MS (Qsight 210, PerkinElmer, USA) (see SI for details). Elution efficiency is calculated as the proportion of measured masses of target psychiatric pharmaceuticals in eluents to their masses adsorbed by the binding gel discs, calculated by the concentration difference of the solution between before and after uptake experiments.

Measurement of Diffusion Coefficients. A diffusion cell device[16] consisting of two stainless steel compartments was used to measure diffusion coefficients, D_{cell}, of the 14 psychiatric pharmaceuticals. A 0.75 mm thick agarose diffusive gel was held in circular windows (diameter 1.5 cm) between the two compartments. 50 mL of 0.01 M NaCl solution containing 1.0 mg L^{-1} psychiatric pharmaceuticals was added to the source compartment, while 50 mL of 0.01 M NaCl solution without pharmaceuticals was added to the receptor compartment. The solution in the two compartments had the same pH (5.63 ± 0.49) and temperatures (25.0 ± 0.5 °C). The solutions were well stirred during a 4 h experiment. Solution samples of 0.2 mL were pipetted from both compartments at 30-min intervals for instrumental analysis. D_{cell} was calculated using eq 2:

$$D_{\text{cell}} = \text{slope}\frac{\Delta g}{CA} \qquad (2)$$

Δg is the thickness of the agarose diffusive gel, C represents concentrations of the psychiatric pharmaceuticals in the source compartment, and A is the area of the

191 window between the two compartments. The slope was evaluated by plotting the
192 diffused masses of the psychiatric pharmaceuticals versus diffusion time.

193 Diffusion coefficients obtained from DGT measurement, D_{DGT}, were also measured
194 to validate the measurement of D_{cell}. Eight DGT devices were deployed in 2.5 L
195 well-stirred solutions containing the 14 psychiatric pharmaceuticals at 20 μg L^{-1} and
196 0.01 M NaCl for 24 h. The concentrations measured by DGT were assumed to equal
197 the solution concentrations, according to the theory of the DGT technique. D_{DGT} was
198 calculated using eq 1.

199 *D* values, D_T, at different temperatures (T, °C) can be calculated from the value
200 at 25 °C (D_{25}), using eq 3[31] as follows:

201 $$\log D_T = \frac{1.37023(T-25) + 8.36\times10^{-4}(T-25)^2}{109+T} + \log\frac{D_{25}(273+T)}{298} \qquad (3)$$

202 **DGT Performance Tests under Different Conditions.** *Effects of pH, IS,* and
203 *DOM.* DGT devices equipped with 0.5 mm thick binding gel (XAD, HLB, or MCX),
204 0.75 mm thick agarose diffusive gel, and 0.015 mm PC filter membrane were used in
205 these validation experiments. To test the effect of pH, IS and DOM on DGT
206 performance, DGT devices were deployed in 2.5 L well-stirred solutions containing
207 psychiatric pharmaceuticals at 20 μg L^{-1} for 24 h and 6 d with: (a) various pH values
208 (changing from 3.02 to 9.45, 0.01 M NaCl, and 0 mg L^{-1} humic acid; pH was adjusted
209 using HCl and NaOH. DGT devices were deployed when the pH of water was
210 completely stable (after 3-4 days), and during the experiment the pH was tested every
211 6 h to ensure its stability; (b) various NaCl concentrations (from 0.0001 M to 0.5 M,
212 pH = 5.72 ± 0.2, and 0 mg L^{-1} humic acid); and (c) various concentrations of humic

213 acid (Aladdin, fulvic acid ≥ 90%) (from 0 to 20 mg L^{-1}, 0.01 M NaCl, and pH = 5.50
214 ± 0.2).

215 *Diffusion Layer Thickness* and *Deployment Time Dependence.* To demonstrate the
216 dependence of mass uptake by DGT devices on the thickness of the diffusion layer,
217 the DGT devices equipped with agarose diffusive gels of different thicknesses
218 (0.5−2.0 mm) were deployed in 2.5 L well-stirred solutions containing psychiatric
219 pharmaceuticals at 20 μg L^{-1} and 0.01 M NaCl at 25 ± 0.5 °C for 24 h. To investigate
220 the dependence on deployment time, the DGT devices were deployed in 7 L
221 well-stirred solutions containing psychiatric pharmaceuticals at 3 μg L^{-1} and 0.01 M
222 NaCl at 25 ± 0.5 °C and retrieved at different times (from 3 to 168 h).

223 Ratios, *R* values, of concentrations measured by DGT, C_{DGT}, to concentrations in
224 water, C_{soln}, should be in the range of 0.9−1.1.

225 **DGT Tests *in Situ* in Field Trials.** Three types of DGT (XAD-DGT containing
226 XAD binding gels, HLB-DGT containing HLB binding gels, and MCX-DGT
227 containing MCX binding gels) were deployed in the Xijiang river, to test the
228 applicability and the robustness of the DGT technique for measuring the 14
229 psychiatric pharmaceuticals *in situ* from a real aquatic system. The Xijiang river, with
230 a length of 2214 km, is the main stream of the Pearl River system, China. Two
231 sampling sites were selected, in Zhaoqing (112°43'12"E, 23°10'12"N) and Zhuhai
232 (113°18'59"E, 22°8'50"N), in the middle reach and the downstream section of Xijiang
233 river, respectively. Standard DGT devices were fixed on a Plexiglass deployment
234 system with the exposure windows outward to ensure that each DGT device had equal

contact with the water (Figure S9). The Plexiglass deployment systems were placed about 1 m below the water surface for 6 days, together with a temperature data logger (iButton DS1921G, Maxim, USA) set to record temperature every 2 h. Each type of DGT device was in triplicate at the same site for the same sampling time. The grab water samples were collected using a Plexiglas water sampler every 2 days during the 6-d DGT deployment (day 0, 2, 4 and 6). The water samples were kept in glass bottles and brought back to the laboratory immediately. Standard deviations were evaluated from the 4 grab samples. DGT field deployments were implemented in August, September and October 2018. There were heavy rains every day from the third day of the August field deployments, and heavy rains every day during the September field deployment. Internal standard of 10 ng $^{13}C_3$-caffeine was spiked in water samples (1 L), and then concentrated with HLB cartridges (Waters, 6 cc 150 mg), which were eluted three times using 3 mL of methanol with 5% ammonia. The eluents were combined and evaporated by blowing down to dryness under nitrogen, then re-dissolving with 1 mL methanol. The final solution was filtered using PTFE filter membranes with 0.22 μm pore size ready for instrumental analysis.

RESULTS AND DISCUSSION

Uptake kinetics and elution efficiencies of the psychiatric pharmaceuticals onto binding gels. Fast uptake of target analytes by the binding gels is the prerequisite for assuring the interface concentration between the binding gel and the diffusive gel is effectively zero, so that equation 1 can be used to obtain DGT measured concentrations accurately.[16] Figures 1 and S2 show that the mass of test

257 pharmaceutical accumulated onto each type of binding gel disc increased rapidly with
258 time in the first 2 h. The adsorbed masses after 3 h were similar to those after 24 h.
259 Uptake rates onto MCX gel discs were faster than those onto XAD and HLB gel discs
260 in the first hour. For example, XAD and HLB gel discs only adsorbed 17% and 39%
261 of the CAF in the original solutions, respectively, while MCX accumulated 47% in
262 the first hour. MCX is a strong cation exchange resin, more suitable for psychiatric
263 pharmaceuticals, which mainly exist as cations in freshwaters. According to Fick's
264 law of diffusion, the minimum uptake amount by the binding gel at the first 5 minutes
265 must not be less than the theoretical diffusion amount through the diffusive gels, to
266 make sure that the uptake of target analytes on binding gel is rapid enough to keep the
267 concentration effectively zero at the binding/diffusive gel interface.[27] In our results,
268 for example, the measured mass of OXA accumulated on XAD, HLB and MCX gel
269 after 5 min (Figure 1) corresponds to a flux of 0.30, 0.22 and 1.15 ng cm^{-2} s^{-1}. The
270 flux through a diffusion layer of a DGT with a 0.765 mm diffusive gel and filter
271 membrane is only 0.07 ng cm^{-2} s^{-1}, when the OXA concentration is 1 mg L^{-1}, which is
272 exceptionally high for natural water bodies including wastewater treatment plants.
273 This indicates the three binding gels all meet the requirement of the DGT technique
274 regarding uptake rates, but MCX had the highest uptake rate for the first few minutes.
275 CAF had similar results, however, XAD may fail to meet the requirement of CAF in
276 long-term deployment, due to its relatively low binding capacity.
277 A stable elution efficiency for a given analyte can precisely evaluate masses taken
278 up by the binding gels and then assure the correct calculation of DGT measured

279 concentrations. Eluents from the XAD, HLB and MCX binding gels contained
280 different percentages of ammonia water, because ammonia can help to release the
281 bound psychiatric pharmaceuticals (data not shown). Although elution efficiencies of
282 XAD and HLB binding gels for most of the studied pharmaceuticals were a little
283 higher than MCX binding gels, all 3 binding gels generally had stable elution
284 efficiencies (Table S3) for different amounts loaded on the binding gels. The elution
285 efficiencies of XAD gels for psychiatric pharmaceuticals ranged from 83 to 97%,
286 similar to values obtained for antibiotics[22] and illicit drugs[32]. Most of the elution
287 efficiencies from HLB binding gels in this study were >80%, but a little lower than
288 those for anionic pesticides[23] and some polar pesticides and antibiotics.[33] Although
289 MCX had lower elution efficiencies for a few tested pharmaceuticals (FHY, 63%;
290 FMA, 55%; and OXA, 63 %), for most compounds the elution efficiencies were in the
291 range 82–100%. The relatively lower elution efficiencies showed the strong binding
292 ability of MCX binding gels to the tested pharmaceuticals.

293 **Diffusion Coefficient Measurements.** Accurate measurement of the diffusion
294 coefficients of target analytes in the diffusion gel is required for calculation of DGT
295 measured concentrations. Masses of the tested psychiatric pharmaceuticals that
296 diffused through the diffusive gel from the source compartment to the receptor
297 compartment of a diffusion cell were linearly correlated (r^2 = 0.997−0.999, at 25°C)
298 with time (Figure S3). Values of D_{cell}, evaluated according to eq 2, are given in Table
299 S4. D_{DGT}/D_{cell} ratios were in the range 0.93−1.13, confirming the reliability of
300 diffusion coefficients measured by both approaches.

DGT Blanks and Method Quantitation Limits. Instrument quantitation limits (IQLs) of UPLC-MS/MS, DGT blank concentrations, and DGT method quantitation limits (MQLs) are listed in Table 1. DGT blank concentrations of the tested psychiatric pharmaceuticals were evaluated by determining the mass of the analytes in XAD, HLB, and MCX binding gels retrieved from DGT device s left in a clean bag without deployment. Concentrations caused by electronic noise of instruments of the tested compounds in the XAD, HLB, and MCX blank gels were low (0–0.13 ng per disc). Only PER had higher masses in the blank gels (0.41, 0.53 and 0.83 ng per disc for XAD, HLB, and MCX gels, respectively). The IQL was the lowest point of the calibration curve which can be quantitatively evaluated within ±20% of its nominal value.[16] MQLs were evaluated from the IQLs, assuming that DGT devices were deployed for 6 days at 25 °C. Similar ranges of MQLs (0.07−-0.97 ng L^{-1}) were obtained for XAD-, HLB-, and MCX-DGT. According to the literature, WWTPs have high concentrations of psychiatric pharmaceuticals. For example, AMI concentrations in some WWTP influents and effluents of Canada were 46−283 and 26−128 ng L^{-1} in 2012[15] and FHY in some WWTP effluents of USA was at 40−73 ng L^{-1} [34] and 20 ng L^{-1} in some WWTP influents of China.[35] Concentrations of BUP in some WWTP influents was 70−191 ng L^{-1} (for Canada)[22] and those of DIA were 33 ng L^{-1} (for Germany)[6]. In surface water, their concentrations were lower than WWTPs, but often >1 ng L^{-1}, i.e. FHY was at 12[34] and 1.4 ng L^{-1} [36] for USA and China and OXA and DIA in Germany was 40[37] and 53 ng L^{-1},[38] respectively. These comparisons indicate that DGT, coupled with UPLC−MS/MS, can meet the required sensitivity for

measurement of psychiatric pharmaceuticals in WWTPs and surface waters. Furthermore, the deployment time can be extended, or more DGT devices deployed and combined into one sample, to improve sensitivity in waters with extremely low concentrations.

Effects of pH, Ionic Strength and DOM on DGT performance. pH, ionic strength (IS), and dissolved organic matters (DOM) are the main aquatic parameters which can influence DGT performance. As shown in Figures 2 and S5a, when solution pH varied from 3 to ~9.5, the ratio, *R* value, of C_{DGT}/C_{soln} basically fell into the acceptable value range of 0.9−1.1 during both 24 h and 6 d deployments, with no significant difference between the three types of DGT devices tested (ANOVA, $p > 0.05$). This shows that pH across the range found in natural waters does not affect sampler performance, so that the DGT can be used to monitor waters of different properties, and in experimental studies where pH/IS/DOM are studied as variables. It is well documented that XAD-DGT can measure illicit drugs[32] and XAD-DGT and HLB-DGT can measure endocrine disrupting chemicals (EDCs)[39] in waters across a similar pH range tested in this study. However, Chen et al.[27] reported C_{DGT}/C_{soln} declined at pH 9.5 when measuring PPCPs using XAD-DGT and HLB-DGT.

When the solution NaCl concentration ranged from 0.0001 to 0.5 M, DGT measurement of all 14 compounds were not affected by the IS during both 24 h and 6 d deployments of DGT (Figures S4 and S5), with the ratio of C_{DGT}/C_{soln} between 0.9 and 1.1. There was no significant difference between the three types of DGT devices (ANOVA, $p > 0.05$). Similar results were obtained in other studies, e.g. on OPFRs

using HLB-DGT with IS varying between 0.0001–0.1 M NaCl,[16] and when measuring EDCs using XAD-DGT and HLB-DGT when IS varied between 0.001 to 0.1 M NaCl.[39] However, when IS increased to 0.5 M NaCl, a significant reduction (>10%) of C_{DGT}/C_{soln} was observed for triclosan (R value = 0.74),[27] some OPFRs (R value = 0.6–0.8),[16] and some EDCs (R value = 0.7–0.8),[39] indicating the influence of IS is related to the physicochemical property of the tested chemicals. In this study, the DGT method for measuring the psychiatric pharmaceuticals can be used in a high IS environment, such as seawaters.

Different from other literature,[16, 26, 27] DOM showed a significant influence on DGT measurement for some psychiatric pharmaceuticals at higher contents of DOM in waters, during both 24 h and 6 d deployments of DGT (Figures S4 and S5). C_{DGT}/C_{soln} values of some of the antidepressants (FHY, RIS, CLO, FMA, MIR, PER, and AMI) declined significantly, when the DOM concentration increased to 12 mg L^{-1} (Figure S4). However, there was no significant influence of DOM on DGT measurement for the other compounds studied with C_{DGT}/C_{soln} values in the expected range of 0.9–1.1. A possible reason for the decline of C_{DGT}/C_{soln} value is that some psychiatric pharmaceuticals can interact with humic acid and become bigger molecules, which lowers their diffusion coefficients. The log K_{ow} of those compounds having low C_{DGT}/C_{soln} values (<0.5) at high DOM concentrations were all >3.5 (except MIR), probably indicating these analytes are more likely be adsorbed by humic acid. Another possible reason is that some pharmaceuticals adsorbed by humic acid cannot be effectively taken up by the binding gels, because of competition between humic

367 acid and binding resins in DGT for the target chemicals. For example, the C_{DGT}/C_{soln}
368 values of FMA measured by MCX-DGT were all in the range of 0.9–1.1, when DOM
369 concentrations were in the range of 0–20 mg L^{-1}, while those of FMA by XAD-DGT
370 and HLB-DGT were < 0.9 when DOM was increased to 8 mg L^{-1} (for XAD-DGT)
371 and 12 mg L^{-1} (for HLB-DGT). When the DOM concentration was 12 mg L^{-1}, there
372 were 6, 5 and 5 analytes measured by XAD, HLB and MCX-DGT that were not in the
373 range of 0.9–1.1. Also, when DOM concentration was 20 mg L^{-1}, there were 7, 8 and
374 6 analytes measured by XAD, HLB and MCX-DGT were not in this range. Generally,
375 MCX-DGT showed a little better performance for the tested pharmaceuticals than
376 other two kinds of DGT, when DOM was in the range of 8–20 mg L^{-1}.

377 **Effects of Diffusive Gel Thickness and Deployment Time.** By transforming eq 1,
378 the adsorbed mass of a target analyte should linearly increase with the reciprocal of
379 the thickness of the diffusive layers (diffusive gel + filter membrane), if a DGT device
380 is deployed in a well-stirred solution with a constant concentration of the analyte and
381 temperature. Figure S6 demonstrates that accumulated masses of the tested
382 compounds are linearly correlated (r^2 = 0.932–0.991, $p < 0.01$) with the reciprocal of
383 the diffusive layer thickness (0.515–2.015 mm). For most of the target analytes, the
384 measured masses were very close to the theoretical line calculated from the solution
385 concentrations using eq 1, indicating accurate DGT measurement of these analytes.
386 However, when the diffusive layer thickness was 0.515 mm, the measured masses of
387 RIS, CAF, MIR, AMI, BUP, and OXA by XAD-DGT and those of RIS, CAF, BUP,
388 and OXA by HLB-DGT were slightly lower than the theoretical line (C_{DGT}/C_{soln}

values between 0.82 to 0.90 for these chemicals), while the phenomenon was not observed for MCX-DGT. This may be attributed to the slower uptake rate of XAD and HLB gels for these chemicals, inducing lower uptake masses when the diffusion flux was high due to a thinner diffusive layer.

For most of the target compounds, DGT measured masses had a linear correlation with increasing deployment time (3−168 h) and fitted well with the theoretical lines predicted from known solution concentrations using eq 1 (Figures 3 and S7). Similar responses to different deployment times were seen when measuring OPFRs[16] and PPCPs[27] using HLB-DGT and PFASs using XAD-DGT.[26] However, some exceptions appeared in this study, for example, measured masses of CAF by XAD-DGT and HLB-DGT deviated from the theoretical lines after 1 or 2 d deployment, respectively (Figure 3). Similar observations were noted for RIS using XAD-DGT and FMA using HLB-DGT. For MCX-DGT, measured responses to all tested psychiatric pharmaceuticals fitted well with the theoretical lines, indicating that MCX-DGT is more suitable for long-term monitoring of psychiatric pharmaceuticals.

Field Trial Application in Xijiang River. Temperatures of the sampling site at Zhaoqing in August, September, and October were 28.5 ± 1.5, 29.0 ± 0.5 and 24.2 ± 0.3°C, respectively, while those at the Zhuhai sampling site were 29.4 ± 1.1, 29.5 ± 0.5, and 25.4 ± 0.9 °C, respectively. pH values at Zhaoqing and Zhuhai were 8.0 ± 0.3 and 8.1 ± 0.1, respectively. Electro-conductivity, which was used to evaluate the ionic strength, was 265–295 and 255–303 μs cm^{-1} at Zhaoqing and Zhuhai, respectively while the electro-conductivity of 1 mM NaCl solution is 111 μs cm^{-1}. Contents of

411 total organic carbon (TOC) were 20–24 and 19–22 mg L^{-1} at Zhaoqing and Zhuhai,
412 respectively. Humic acid only contributes a part of TOC in natural waters.
413 Concentrations of humic acid were 10–12 mg L^{-1} and 9.5–11 mg L^{-1} converted
414 according to other literature based on the TOC contents.[40] This is similar to previous
415 reports for the Xijiang River.[41, 42] In summary, the environmental parameters in the
416 grab samples were consistent with the conditions used for DGT characterization in the
417 lab.

418 Figure 4 and Table S8 presents concentrations obtained from the grab samples and
419 from DGT in August, September, and October. Most of the target psychiatric
420 pharmaceuticals can be detected at the two sampling sites. The percentage of target
421 analytes detected with DGT was consistent with the grab sampling. CAF had the
422 highest concentration of ~300 ng L^{-1}. It is a compound which is also used as a food
423 additive. Sometimes FHY, RIS, and MIR were present in the 10–100 ng L^{-1} range.
424 Concentrations of other target analytes were mostly <10 ng L^{-1}. Most of the
425 DGT-measured concentrations matched the mean values of grab samples with the
426 C_{DGT}/C_{grab} values of 0.9 to 1.2. Though the sampling frequency of the grab sampling
427 was not high, the comparison between DGT measurement and grab sampling suggests
428 DGT has a good ability to perform in field. [16, 39] Concentrations measured by HLB-
429 and MCX-DGT were more consistent with the mean value of grab samples. During
430 our sampling periods, there were several heavy rainstorms and flooding caused by
431 seasonal typhoons, which will cause variations in the concentrations of target
432 compounds. By contrast, DGT measures time averaged concentrations conveniently

433 and efficiently.

434 For most of the studied analytes, concentrations in August and September were
435 higher than in October, maybe due to the heavy rainfall caused by the summer
436 monsoon in August and September. There are several cities and tributaries around the
437 two sampling points. Those cities all have several municipal sewage treatment plants
438 and rain water outlets, and some of them have pharmaceutical factories which
439 produce psychiatric pharmaceuticals. These are possible sources of psychiatric
440 pharmaceuticals in Xijiang River. Psychiatric pharmaceuticals are readily adsorbed on
441 soils because of their high K_{ow}. During rainy weather there are often floods in cities
442 which may cause pollutants to flow out from drains and sewage collection facilities,
443 bringing the contaminants from soils and tributaries to the main stream. No obvious
444 difference was found in distribution and variation of the target chemicals between the
445 sampling sites. Further field investigations are needed to clarify the sources of the
446 analyte psychiatric pharmaceuticals.

447 **Environmental Implications.** The MCX binding layer performed best overall of
448 the 3 resins tested for a new DGT suitable for psychiatric pharmaceuticals. From the
449 comparison of the three resins, we infer that XAD and HLB-DGT can be used to
450 measure other psychiatric pharmaceuticals and their break-down compounds, while
451 MCX-DGT is the most suitable for these cationic compounds. Future work should
452 address development of DGT to sample parent and breakdown products of psychiatric
453 pharmaceuticals. This approach has recently been developed for the pesticide atrazine
454 and its breakdown products.[43] The DGT sampler is shown to be suitable for different

455 environmental conditions between pH 3–9.5, ionic strength 0.0001–0.5 M and DOM
456 <12 mg L^{-1}. Given the uptake rates, typical environmental concentrations and typical
457 instrument detection limits of the target analytes, the recommended deployment time
458 of DGT devices is >5 days.

459 The field deployment showed that concentrations determined with DGT are similar
460 to traditional spot/grab sampling, proving that DGT is a reliable method for in situ
461 measurement of psychiatric pharmaceuticals. During the field sampling period,
462 seasonal typhoons brought heavy rainstorms and flooding in Xijiang River and hence
463 water fluxes and levels sharply increased, leading to variations in concentrations of
464 psychiatric pharmaceuticals. The extreme weather events will bring risks for sampling
465 workers who took grab samples. DGT monitoring can avoid the issue of safety
466 problem in the extreme weather events and provide valuable data on the target
467 chemicals during this dangerous period to understand the impact of the event on
468 chemical concentrations. In addition, there may be cases where concentrations of
469 psychiatric pharmaceuticals in rivers vary with time due to episodic discharges. DGT
470 will be a better technique in these conditions as it measures the time weighted average
471 concentrations. The newly developed method has the potential for identifying source
472 and dispersal events of the chemicals, for monitoring campaigns and for
473 understanding the biogeochemical behaviour of psychiatric pharmaceuticals, such as
474 their transport mechanisms and their fate in sediments.

475 # ASSOCIATED CONTENT

476 **Supporting Information**

Detailed information on tested chemicals, analytical methods and QA/QC; detailed information on methods to check potential adsorption onto materials, aging effect, binding capacity and competing effect; results and discussion on potential adsorption onto materials, aging effect. binding capacity and competing effect; and tables and figures of potential adsorption onto materials, elution efficiencies, diffusion coefficients, uptake kinetics, effects of IS, DOM, diffusive gel thickness, deployment time, and storage time of binding gel on DGT performance, binding capacity and competition effect.

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606 **Table 1.** DGT blanks (3 types of binding gels), instrument quantitation limits (IQLs)
607 of targets detected by UPLC−MS/MS, D_{cell} values, and method quantitation limits
608 (MQLs) for DGT during field application.

Analytes	DGT blank, ng/disc, (mean ± SD), n = 9			IQL, μg /L	D_{cell} at 25 °C, 10^{-6} cm^2 /s	MQL, ng /L		
	XAD	HLB	MCX			DGT		
						XAD	HLB	MCX
FHY	0.05±0.02	0.06±0.04	0.13±0.07	0.02	4.27	0.10	0.130	0.177
RIS	0.02±0.03	0.03±0.03	0.02±0.02	0.02	4.90	0.077	0.062103	0.097
CAF	0.1±0	0.1±0	0.08±0.02	0.02	6.42	0.143	0.08	0.07
CLO	0.03±0.03	0	0.04±0.03	0.04	3.57	0.123	0.157	0.147
FMA	0.05±0.02	0.02±0.01	0.07±0.02	0.02	4.44	0.093	0.150	0.193
MIR	0.04±0.02	0.08±0.01	0.04±0.03	0.02	5.22	0.10	0.103	0.09
PER	0.41±0.07	0.53±0.07	0.83±0.12	0.1	3.05	0.850	0.883	0.867
AMI	0	0	0	0.02	4.76	0.107	0.110	0.113
BUP	0	0	0	0.02	5.21	0.110	0.058097	0.107
EST	0.02±0.01	0.02±0	0	0.02	5.20	0.097	0.103	0.10
DIA	0	0	0	0.02	5.10	0.097	0.106	0.110
TEM	0.05±0.03	0.02±0.02	0	0.02	5.05	0.10	0.110	0.113
ALP	0	0	0	0.02	4.76	0.113	0.130	0.130
OXA	0.04±0.04	0.03±0.01	0.05±0.02	0.02	4.98	0.10	0.107	0.150

609 MQL was calculated using the equation: $\mathrm{MQL} = \frac{\mathrm{IQL}}{\mathrm{fe} \times \mathrm{CF}}$. For DGT, f_e is the elution efficiency, CF
610 is concentration factor and calculated using the equation: $\mathrm{CF} = \frac{\mathrm{DA}t}{\mathrm{V}\Delta\mathrm{g}}$, V is concentrated volume of
611 elution solution (0.5 mL). Here it is assumed a DGT device with a 0.015 mm thick PC filter
612 membrane, a 0.75 mm thick agarose diffusive gel, and a 0.5 mm thick binding gel was deployed
613 for 6 d at 25 °C.

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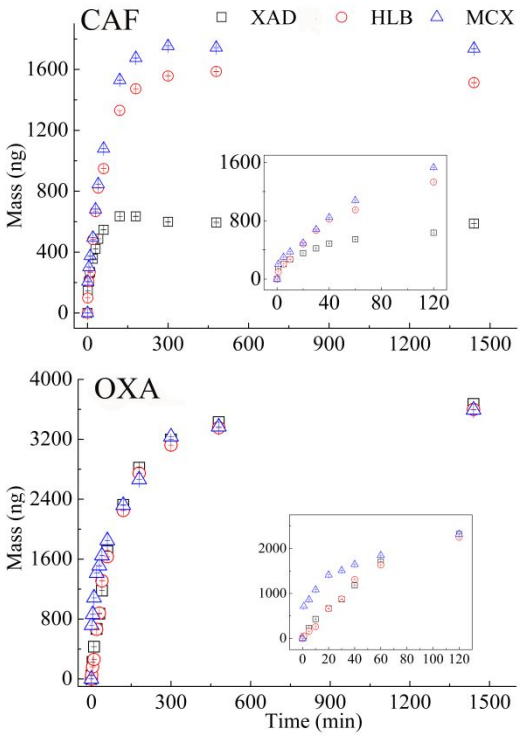
615



616

617 **Figure 1.** Masses of CAF (caffeine) and OXA (oxazepam) adsorbed by XAD, HLB,

618 and MCX binding gel discs (in 40 mL solutions containing 0.01 M NaCl and tested

619 CAF and OXA at 100 μg L^{-1}) plotted against shaking time from 0.5 min to 24 h. Error

620 bars were calculated from the standard deviations of three replicates.

621

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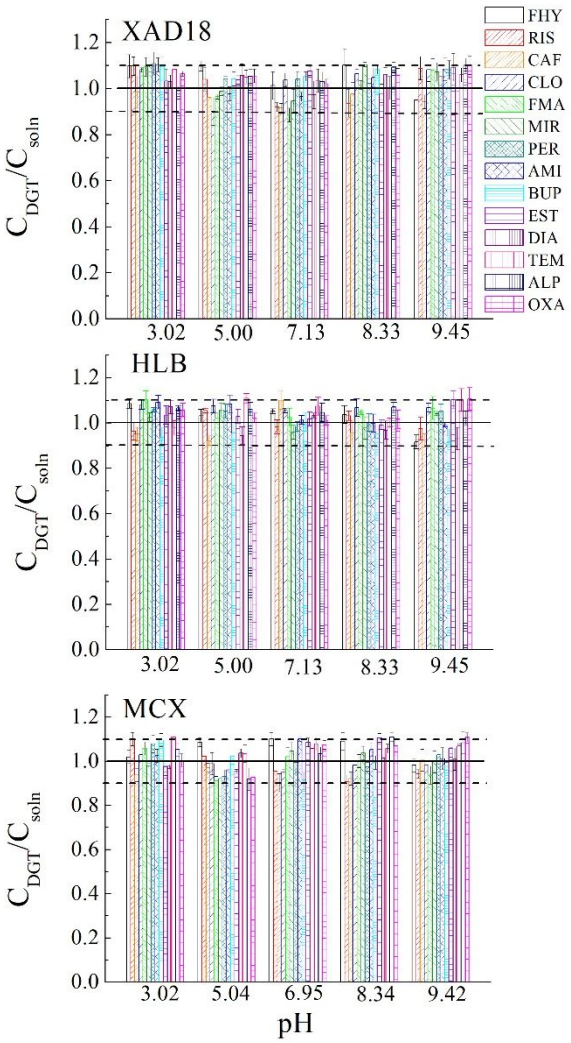

623

624 **Figure 2.** Effect of pH on the performances of XAD-DGT, HLB-DGT, and
625 MCX-DGT devices (n=3). The solid line and dotted lines mean target C_{DGT}/C_{soln}
626 values of 1 ± 0.1. Error bars are calculated from the standard deviation of three
627 replicates.

628

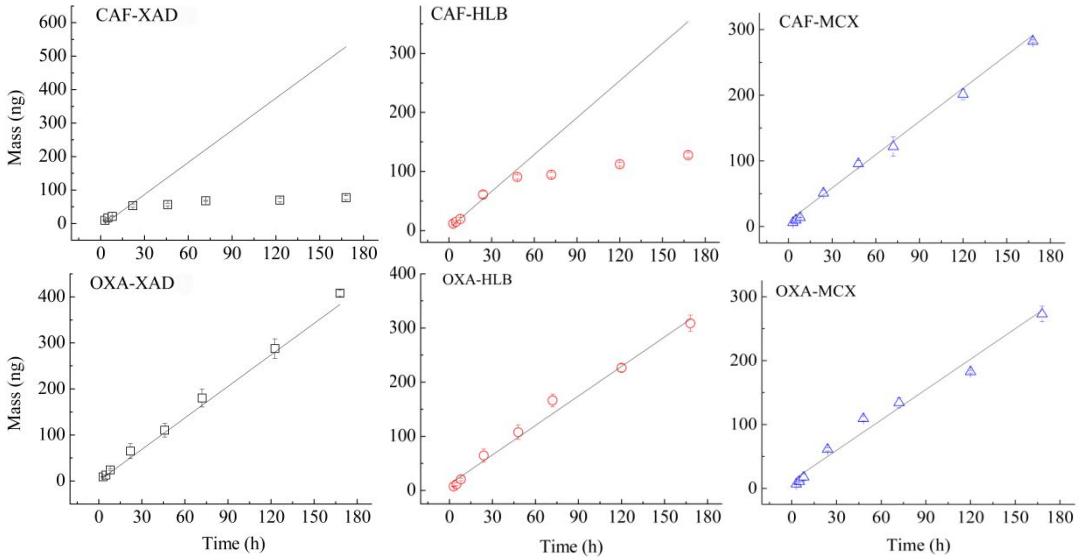

Figure 3. Measured masses of CAF (caffeine) and OXA (oxazepam) accumulated by DGT devices containing XAD, HLB and MCX binding gels with the deployment time. DGT devices deployed in 7 L well-stirred solutions containing 0.01 M NaCl and tested psychiatric pharmaceuticals at 3 μg L^{-1} for different deployment times (3–168 h). pH was 5.65 ± 0.2 and the temperature was 25 ± 0.5 °C. The solid line represents the theoretical values predicted from the known solution concentrations using eq 1. Error bars are calculated from three replicates.

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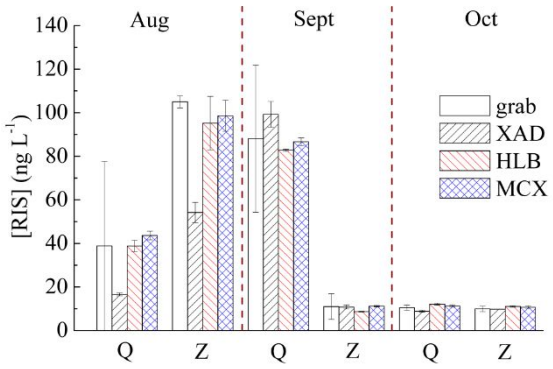


639

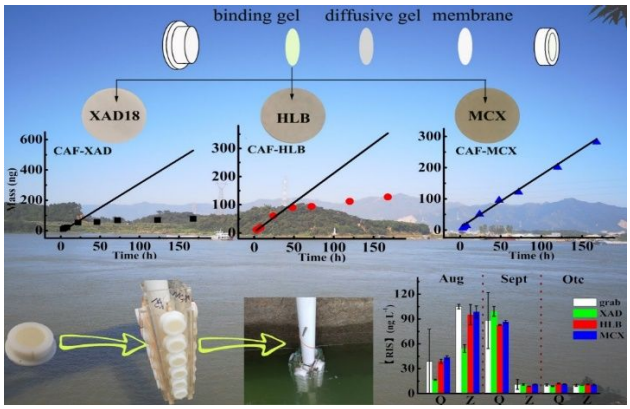
640 **Figure 4.** RIS (risperidone) concentrations measured by grab sampling and with DGT

641 at Zhaoqing and Zhuhai sampling sites in August, September, and October 2017. Q =

642 the sample site at Zhaoqing, while Z = the sample site at Zhuhai.

643

644 For TOC art only

645 

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