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Development and applications of diffusive gradients in thin films for monitoring pharmaceuticals in surface waters

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Abstract

Pharmaceutical contaminants in surface water have raised significant concerns because of their potential ecological risks. In particular, coronavirus disease 2019 (COVID-19)-related pharmaceuticals can be released to surface water and reduce environmental water quality. Therefore, reliable and robust sampling tools are required for monitoring pharmaceuticals. In this study, passive sampling devices of diffusive gradients in thin films (DGTS) were developed for sampling 35 pharmaceuticals in surface waters. The results demonstrated that hydrophilic-lipophilic balance (HLB) was more suitable for DGT-based devices compared with XAD18 and XDA1 resins. For most pharmaceuticals, the performance of the HLB-DGT devices were independent of pH (5.0–9.0), ionic strength (0.001–0.5 M), and flow velocity (0–400 rpm). The HLB-DGT devices exhibited linear pharmaceutical accumulation for 7 days, and time-weighted average concentrations provided by the HLB-DGT were comparable to those measured by conventional grab sampling. Compared to previous studies, we extended DGT monitoring to include three antiviral drugs used for COVID-19 treatment, which may inspire further exploration on identifying the effects of COVID-19 on ecological and human health.

1. Introduction

Regarding emerging contaminants, pharmaceuticals have raised significant concerns about their common occurrence and potentially deleterious effects on the health of ecosystems and humans (Santos et al., 2010). As surface water is the main sink of pharmaceuticals, the concentrations of pharmaceuticals in surface water have been studied extensively using various techniques (Xiang et al., 2021). Because of the poor removal efficiency in wastewater treatment plants (WWTPs) (Zhang et al., 2017), the concentrations of pharmaceuticals detected in surface water varied from ng L⁻¹ to μg L⁻¹. Hence, it is pivotal to obtain accurate concentrations of pharmaceuticals in riverine environments to fully understand the effects of pharmaceutical exposure. The availability of effective tools is important for chemical contaminant monitoring. Conventional grab sampling is the predominant sampling method for evaluating the concentration of micropollutants in surface water (Novic et al., 2017). However, low-frequency grab sampling cannot detect fluctuating concentrations over extended event durations (Mutzner et al., 2019). Furthermore, high-resolution grab sampling increases the cost and labor of monitoring contaminants. Since target pollutants are preconcentrated during deployment, passive sampling methods have been proposed as alternative options owing to improved detection limits and reduced measurement uncertainty (Montero et al., 2012). Polar organic chemical integrative sampling (POCIS), Chemcatcher, and diffusive gradients in thin films (DGT) are the three most common passive samplers for monitoring polar organic contaminants (Alvarez et al., 2004). However, using POCIS and Chemcatcher results in large variations in time-weight average (TWA) concentration calculation due to the choice of a single sampling rate (Pouliot et al., 2014). Compared to POCIS and Chemcatcher, contaminant uptake by DGT is independent of
hydrodynamic conditions, and no extra calibration is required for in situ monitoring (Davison and Zhang, 1994). Therefore, DGT is suitable for providing quantitative in situ measurements of micropollutants in environmental waters.

DGT has been applied to the measurement of a broad range of organic pollutants, including pesticides (Guibal et al., 2017), pharmaceuticals (Challis et al., 2018; Chen et al., 2012; Chen et al., 2013; Xie et al., 2018; Xie et al., 2021; You et al., 2020; You et al., 2019), household and personal care products (Chen et al., 2017), synthetic musks (Ren et al., 2020), perfluoroalkyl substances (Fang et al., 2021; Guan et al., 2018), endocrine-disrupting chemicals (Chen et al., 2018; Guo et al., 2017b; Guo et al., 2019), illicit drugs (Guo et al., 2017a; Zhang et al., 2018), organophosphate esters (Wang et al., 2019), brominated flame retardants (Feng et al., 2019), bisphenols (Zheng et al., 2015), bitter agent (Liu et al., 2021a), and melamine (Liu et al., 2021b). Although these pioneering studies extended the use of DGT to monitor organic chemicals, model contaminants have remained limited. Thus, it is important to understand any constraints that apply to pollutants with different chemical properties in DGT applications (Wang et al., 2019), and more work is still needed to reveal the optimal configuration of DGT and the factors that impact sampling performance. Previous studies demonstrated the development of DGT for some pharmaceuticals in wastewater (Challis et al., 2016; Chen et al., 2015; Chen et al., 2015). However, little is known about the performance of DGT in pharmaceutical monitoring in surface waters.

In this study, we aimed to develop DGT devices for the monitoring of pharmaceuticals in surface waters. We selected high-priority pharmaceuticals identified for monitoring and risk assessment in multiple prioritization exercises (Bu et al., 2021; Bu et al., 2020; Howard and Muir, 2011; Huang et al., 2022; Li et al., 2019). Recently, the outbreak of coronavirus disease 2019 (COVID-19) has become a global health emergency (Fang et al., 2020). Three antiviral drugs (lopinavir, ritonavir, and arbidol) have been used to control the spread of COVID-19 (Fang et al., 2020; Li et al., 2021). During the COVID-19 pandemic, the consumption of antiviral drugs sharply increased, posing high risks to the aquatic ecosystem (Kumari and Kumar 2022; Nannou et al., 2020). Yao et al. (2021) and Kumari and Kumar (2022) validated the high ecological risks to the aquatic environment caused by ritonavir and lopinavir. Ul’yanovskii et al. (2022) found a pronounced accumulation of arbidol in river bottom sediments, which could be a source of secondary pollution. The impacts of the pharmaceuticals used for COVID-19 treatment on the aquatic environment are of increasing concern and merit further investigation (Bandala et al., 2021). Therefore, developing a DGT passive sampling device for monitoring antiviral drugs used for the treatment of COVID-19 is required for the quantitative assessment of ecological risks resulting from the COVID-19 pandemic.

To develop DGT devices, we systematically tested the uptake kinetics and binding capacity of various binding resins, determined the diffusion coefficients in diffusive gels, and tested the potential adsorption of target pharmaceuticals on membrane filters. Consequently, the influences of pH, ionic strength (IS), and flow velocity on DGT sampling were evaluated. Finally, the developed DGT devices were deployed in the field to evaluate the performance compared to that obtained by grab sampling.

2. Materials and methods

2.1. Chemicals and reagents

Thirty-five target pharmaceuticals were selected for potential monitoring purposes based on their inherent properties, such as persistence, bioaccumulation, toxicity, and risk estimates (Bu et al., 2021; Bu et al., 2020). These pharmaceuticals covered 25 antibiotics and 10 non-antibiotics, including three antiviral drugs used for COVID-19 treatment. The target antibiotics fell into six categories, including β-lactams, macrolides, fluoroquinolones, sulfonamides, tetracyclines, and other antibiotics, as follows: ampicillin (AMP), azithromycin (AZM), chloramphenicol (CAP), ciprofloxacin (CIP), doxycycline (DC), enrofloxacin (ENR), erythromycin (ERY), florfenicol (FF), lincomycin (LIN), norfloxacin (NOR), ofloxacin (OFL), oxytetracycline (OTC), pefloxacin (PEF), roxithromycin (ROX), sulfadiazine (SD), sulfadimidine (SFM), sulfamerazine (SMZ), sulfamethoxazole (SMX), sulfanomethoxime (SMM), sulfapyridine (SP), tetracycline (TC), trimethoprim (TMP), rifaximin (RIF), griseofulvin (GRI), and clarithromycin (CTM). The non-antibiotics fell into eight categories, including the antiviral agent, hypoglycemic, blood lipid regulator, anticonvulsant drug, anti-inflammatory drug, antidepressant, antiplatyhelmintic drug, and antirheumatic drug, as follows: bezafibrate (BZF), carbamazepine (CBZ), clofibrate (CLOA), diclofenac (DIC), fluoxetine (FXT), gemfibrozil (GEM), nicosamide (NIC), arbidol (ARB), ritonavir (RTI), and lopinavir (LOP). An isotope-labeled internal standard contained sulfadimidine-d₄ (SFM-d₄), carbamazepine-d₁₀ (CBZ-d₁₀), roxithromycin-d₇ (ROX-d₇), chloramphenicol-d₄ (CAP-d₄), norfloxacin-d₉ (NOR-d₉), and demeclocycline (DEM). Further details of all reagents are provided in Text S1 of supporting information. The physicochemical properties, class types, and structures of target pharmaceuticals are provided in Table S1.

2.2. Preparation of DGT devices

A standard DGT device is composed of a binding resin (thickness: 0.5 mm) for the adsorption of target analytes, a diffusive gel layer (thickness: 0.8 mm) allowing free diffusion of analytes, a membrane filter (0.45 μm) to protect the gel layer from mechanical destruction, and a standard plastic molding for housing the gel layer and the membrane filter, with a window area of 3.14 cm² (Fig. S1). Three binding resins, namely hydrophilic–lipophilic balance (HLB), XAD18, and XDA1, together with two diffusive gels including polycrylamide gel (PA gel, 0.8-mm thick) and agarose gel (AG gel, 1.5% agarose, each 0.8-mm thick) were selected to test their suitability for monitoring. The HLB sorbent was broadly used in the determination of pharmaceuticals in water using solid-phase extraction (SPE) and can interact with both apolar and polar organic molecules (Biakli-Bielinska et al., 2016). XAD18 resins have a good performance in binding many compounds with a wide diversity of chemical properties (Guibal et al., 2019). Xie et al. (2018) reported that XAD1 resin has high adsorption capacity for antibiotics. Both XAD18 and XDA1 were non-polar resin, the specific surface area of XDA-1 (1279 m² g⁻¹) was higher than XAD18 (800 m² g⁻¹), while the average aperture of XAD18 (150 nm) were much higher than XDA1 (30 nm) (Xie et al., 2018). These binding gels and diffusive gels were prepared according to previously reported procedures (Zhang and Davison, 1999). Details about gel making are described in Text S2.

2.3. DGT theory

The DGT measurement, C_DGT, provided the TWA concentrations of organic pollutants in the solution using the following equation, which was derived from Fick’s first law of diffusion: The concentrations of target pharmaceuticals accumulated by DGT can be calculated by Eq. (1) (Davison and Zhang, 1994):

\[ C_{DGT} = \frac{M (\Delta g + \delta)}{DA_t} \]  

where M is the mass of the analyte in the binding gel (ng), Δg is the diffusive layer thickness (cm), D is the diffusion coefficient of the analyte in the diffusive gel (cm² s⁻¹), t is the deployment time of DGT devices (s), and A is the DGT sampling area exposed to the bulk solution (cm²). δ is the thickness of the diffusive boundary layer (DBL, cm). Under well-stirred conditions, δ can be neglected (Davison and Zhang, 2012). The effect of flow velocity on DGT uptake is discussed in Section 3.5.2.
2.4. DGT performance testing

A series of tests were conducted to develop the DGT devices. These include (1) the potential adsorption of target pharmaceuticals to DGT assemblies and (2) the determination of the diffusion coefficients of target pharmaceuticals. Details of the method and the calculation technique are provided in Text S3. The measured $D$ values for target pharmaceuticals at different temperatures are listed in Tables S2 and S3. In addition, (3) uptake kinetics and binding capacity tests of binding resins and (4) the determination of elution efficiencies of target analytes was conducted. Extraction procedures are described in Text S3. The elution efficiencies under different concentrations are given in Table S5. (5) The performance of DGT devices was subsequently tested for the effects of pH, IS, and flow velocity. (6) The effects of exposure time and diffusion layer thickness on DGT uptake were evaluated.

2.5. In situ application of DGT in the field

To verify the reliability of DGT measurements in surface waters, the DGT devices were deployed in two rivers in Beijing in December 2021 for a week. As shown in Fig. S2, a total of four sampling sites (S1–S4) were located in the Beixiao River and the Tonghui River in Beijing. To validate whether the DGT devices maintained the linear uptake of target pharmaceuticals during short-term exposure, another sampling campaign including a 7-day continuous grab and DGT sampling was conducted at the S1 site. To improve DGT sensitivity, parallel DGT devices were deployed and pooled as one sample at a depth of 30 cm at each site. During the first campaign, 9 DGTs (3 × 3) were deployed and 3 DGTs pooled as one sample for 7 days at each sampling site. During the second campaigns, the 9 DGTs were retrieved in triplicate day by day, 3 DGTs are pooled together to extract.

After sampling (Fig. S1(f), (g)), the DGT was rinsed and immersed with Milli-Q water and then sealed in a clean plastic bag for transport at 4 °C. In parallel, grab samples were also collected after 1, 3 and 7 days during the DGT deployment period using 2-L precleaned amber bottles. Details about water sample collection and extraction for grab and DGT samples were given in Text S4. Temperatures and the flow velocity were recorded during the deployment period. Further information about water quality parameters is provided in Table S6.

2.6. Chemical analysis and quality assurance/quality control (QA/QC)

All samples were analyzed using a high-performance liquid chromatography-tandem mass spectrometer (HPLC-MS/MS, Shimadzu, Kyoto, Japan) with electrospray ionization (ESI) to determine the target pharmaceuticals. The optimized mass spectrum parameters, retention time, and the internal standard are provided in Table S7. The instrument limits of detection (IDLs) and quantification (LOQs), DGT blank concentration, and DGT method detection limits (MDLs) of target pharmaceuticals are listed in Table S8. The details of the analysis procedures are provided in Text S5.

3. Results and discussion

3.1. Adsorption test and selection of DGT materials

To accurately measure the target pharmaceuticals by DGT devices, their potential sorption onto components used for DGT devices, except for binding resins, should be negligible. Here, four types of membrane filters (nylon, PES, hydrophilic PTFE, and PCTE), together with DGT moldings (including base and caps) and diffusive gels (AG and PA gels), were assessed for the possible adsorption of target pharmaceuticals. Fig. S3 shown that the maximum adsorption of the target analytes was detected for nylon membranes (>98%), followed by PES membranes (>94%). On the contrary, the pharmaceuticals barely adsorbed on hydrophilic PTFE membranes (<8%). Macrolide antibiotics showed moderate adsorption on PCTE membranes, whereas FXT (61.6%) substantially adsorbed on PCTE membranes. For diffusive gels, the target pharmaceuticals were not adsorbed appreciably on the AG gel (<3%), whereas significant adsorption was observed on the PA gel for three target analytes in the range of 21.4%–38.9% (SMX, GRI, and ARB). Chen et al. (2012) also found that SMX significantly adsorbed on PA gels. There was little adsorption of target pharmaceuticals on DGT moldings (<17%). Hence, the AG gel and the PTFE membrane were selected for use in subsequent experiments.

3.2. Diffusion coefficients of target pharmaceuticals

The $D$ values are a key factor for calculating TWA concentrations. As shown in Fig. S3, the mass of the target pharmaceuticals diffusion on the AG gel displayed a good linear relationship with time ($R^2 = 0.9781–0.9999$). Due to the low linearity of the diffusion curve ($R^2 < 0.7$) for seven target pharmaceuticals (ARB, SMX, AZM, FXT, GEM, CAP, and OTC), the $D$ values of these pharmaceuticals were calculated from time series deployment of HLB-DGT devices in the known spiked solution. This method showed good agreement with the diffusion cell method (Guan et al., 2015; Guibal et al., 2017; Zou et al., 2018). The results indicated that the mass of the seven target analytes accumulated by the HLB-DGT devices increased linearly with the deployment time (Fig. S5). The $D$ values at 25 °C were in the range of $1.21 \times 10^{-6}–5.22 \times 10^{-6} \text{ cm}^2 \text{s}^{-1}$. The $D$ values at other temperatures were estimated using Eq. S3 and shown in Tables S2 and S3.

As shown in Table S4, the scale of the $D$ values for common antibiotics agreed with the results of the DGT accumulation method for seawater determined by Xie et al. (2018). The slight difference could be owing to a higher IS. The measured $D$ values in the present study were also consistent with the result for freshwater determined by Chen et al. (2013). The measured $D$ values for four non-antibiotics (CBZ, CLOA, GEM, and FXT) were in line with the findings of Stroski et al. (2018), who used PA gel in the diffusion cell experiment. However, the results in the present study were less than those reported by Challis et al. (2016), differing by a factor of 1.17 (range: 1.13–1.21) across the common non-antibiotics. Generally, $D$ values measured by the diffusion cell method was lower than those determined by the slice stacking method (Bonnaud et al., 2022). It is expected that the measured $D$ values of common pharmaceuticals in the present study were lower than those of Bonnaud et al. (2022) with a factor of 1.62 (range: 1.02–2.83). This bias could be reduced by increasing the gel thickness or estimate the DBL thickness in the diffusion cells method. The discrepancy in the measured $D$ values may be ascribed to the analytical deviation (Bonnaud et al., 2022), different equations in slice stacking method (Amato et al., 2018; Bonnaud et al., 2022) and OTC, the measured $D$ values may be ascribed to the analytical deviation (Bonnaud et al., 2022), different equations in slice stacking method (Amato et al., 2018; Bonnaud et al., 2022) and potential diffusion on the diffusion cell (Wang et al., 2019). Even for the same target pharmaceutical, the adsorption characteristics of diffusion cells wall made of different materials are different, which may affect the diffusion coefficient to a certain extent. Therefore, it is necessary to increase the sampling frequency to ensure the concentrations in source compartment stable throughout the diffusion experiment.

3.3. Kinetic uptake and binding capacity

The results of binding kinetics demonstrated that the adsorbed mass of the target pharmaceuticals on the three resins rapidly increased with the exposure time for the first hour, followed by more gradual uptake (Fig. 1 and Fig. S6). For the most target pharmaceuticals, the uptake by the HLB resin gel was slightly faster than that of the XAD18 and XDA1 resin gels. These results illustrated that the HLB gel can bind to target analytes more quickly since the interface concentration between the binding gel and the diffusive gel was zero during deployment, which is the prerequisite for highly accurate DGT measurements.

The affinity of binding resins to target analytes is an important factor to reliably measure target pharmaceuticals. The three resins had high...
Fig. 1. Binding kinetics of target pharmaceuticals by HLB, XAD18, and XDA1 gels. The error bars were calculated from the standard deviation of three replicates.
affinity to most target analytes. The order of ability to bind the target pharmaceuticals was HLB > XDA1 > XDA18 (Table S9). HLB resins displayed nearly 100% adsorption for most pharmaceuticals, while XDA18 and XDA1 gels showed less than 60% binding efficiency to the three pharmaceuticals (SD, SMX, and AMP). Combined with the kinetic uptake and binding efficiency of the three resins to the target analytes, HLB binding gels were more suitable for use in the field. Therefore, HLB binding resins were finally selected for standard DGT devices in this study.

The adequate linear binding capacity is key to obtaining the TWA concentration of target analytes accurately. The accumulated mass of target pharmaceuticals onto HLB-DGT devices initially increased linearly with the solution concentration (Fig. S7). The capacities of HLB-DGT for all pharmaceuticals ranged from 1.21 (AMP) to 8.92 (RIT) μg/gel (Table S10). According to the maximum linear binding capacities, the maximum water concentrations measured by HLB-DGT were in the range of 3.51–48.2 μg L⁻¹ for a deployment time shorter than a month (Table S10). The results were far greater than the reported concentrations in surface water (Xiang et al., 2021). Therefore, HLB-DGT is suitable for long-term monitoring of target analytes in the field.

### 3.4. Extraction efficiencies

Previous studies demonstrated acetonitrile (ACN) can effectively elute a diversity of organic pollutants (Chen et al., 2017; Chen et al., 2018). Thus, ACN was used as an eluent. To simplify the elution procedures, elution conditions were determined by comparing the efficiencies under two elution doses (5 mL or 10 mL) in 30-min ultrasonic extraction. The results showed that 30-min ultrasonic extraction using 10-mL ACN provided good recoveries that ranged from 68% (TC) to 120% (RIT) for most target pharmaceuticals (Fig. S8). As shown in Table S5, a stable recovery was achieved with a wide range from 60.9% to 110% for all pharmaceuticals in the investigated concentration range (10–200 μg L⁻¹). The developed one-step elution procedure appreciably improved the elution efficiency. Therefore, 30-min ultrasonic extraction using 10-mL ACN was selected for the extraction method.

### 3.5. DGT performance characteristics under different conditions

#### 3.5.1. Effect of pH and ionic strength

The concentrations measured by HLB-DGT for the majority of test pharmaceuticals were not significantly affected by pH in the range of 6.5–8, suggesting that HLB-DGT can be directly applied in most of the surface water field conditions in this pH range (Fig. 2(a) and Fig. S9). However, some ionizable analytes appeared to demonstrate a strong pH-dependent uptake, which was also validated by Jeong et al. (2017). For example, LIN (pKa = 12.37) and ERY (pKa = 8.8) exhibited the most appreciable reduction in HLB-DGT uptake at pH = 5. The same phenomenon, but in reverse, was observed for DC and five sulfonamide antibiotics (SD, SFM, SMM, SMZ, and SP). For these pharmaceuticals, the ratio of \( C_{DGT}/C_0 \) deviated from 0.8 in the pKa range of 1.4–7.49 in pH = 9, which is similar to the finding of Stroski et al. (2018). The HLB resin has a higher capacity and affinity to neutral species compared to ionized species due to sorption mechanisms was greatly affected by analyte speciation (Bäuerlein et al., 2012). Although pH affected the HLB-DGT uptake of a few target pharmaceuticals, this effect was negligible in a weak alkaline environment. Further research must be conducted toward exploring the effects of pH on the HLB-DGT devices in the future.

The effects of various IS (0.001–0.5 M) on the HLB-DGT uptake of target pharmaceuticals were investigated (Fig. 2(b) and Fig. S10). By measuring the initial concentration under different IS conditions (n = 5), it was found that the initial concentration under high IS was lower than that under low IS for some analytes, which may be attributed to the solubility of the target analytes reduced by the “salting-out” effect (Xie et al., 1997). However, this phenomenon did not significantly affect the HLB-DGT uptake performance. The ratio of \( C_{DGT}/C_0 \) was within acceptable limits (1.0 ± 0.2), even at a relatively high IS (0.5 M), for all target pharmaceuticals except for CLOA. High IS decreased the uptake of CLOA onto the HLB gels because of the availability of less free dissolved species. Xie et al. (2018) proposed that the difference in the measured D values under various IS conditions could further influence the \( C_{DGT}/C_0 \) values. When the IS changed dramatically, whether the D values of target analytes can be affected need further verification. Overall, the results indicated no significant effects of IS on the HLB-DGT performance for most analytes. Thus, the HLB-DGT devices are suitable for use in surface water.

#### 3.5.2. Effect of flow velocity and diffusive boundary layer

The variation of flow velocity could introduce uncertainty in TWA measurements. Thus, to clarify the effect of flow velocity on the HLB-DGT performance, sampling using HLB-DGT at different stirring rates was conducted. Under unstirred conditions, all target pharmaceutical concentrations were appreciably underestimated by 42.7% (range 32.8%–58.1%) (Fig. 3 and S11). For some target pharmaceuticals, the water concentrations were still underestimated by <20% when the flow velocity reached 50 rpm. While with the flow velocity further increased,
the CDGT/Cb was within 1.0 ± 0.2 for all pharmaceuticals and did not change significantly. The results indicated that the DBL decreased with the increased flow velocity. The thickness of the DBL (δ) at different stirring rates can be estimated using Eq. (2):

$$\delta = \frac{CDGT \cdot DAt}{M} - \Delta g$$  

(2)

where the thickness of the diffusive gel (Δg) used in the experiment was 0.8 mm. M denotes the accumulated mass on HLB-DGT at different stirring rates.

The results showed that δ was in the range of 0.060 ± 0.013 cm under static conditions and δ = 0.028 ± 0.007 cm under low-flowing conditions (Table S11), which were consistent with the results reported by Challis et al. (2016) and Chen et al. (2013), who used another well-documented method to calculate the DBL thickness (Uher et al., 2013). It was found that δ decreased significantly for the target pharmaceuticals from static conditions to minimal stirring (50 rpm) and further reduced as the stirring rates increased. Under more turbulent flow (200, 400 rpm), δ remained stable (δ = 65 ± 19 μm), indicating that the effect of DBL can be ignored for well-stirred conditions. To reduce the errors in the TWA concentrations, 0.028 cm was subsequently used as the DBL thickness to calculate CDGT in surface water.

3.5.3. Time and diffusion layer thickness dependence

The results (Fig. 4 and S12) displayed that the accumulated masses of test pharmaceuticals by the HLB-DGT devices for the deployment time of 5 days agreed well with the theoretical prediction line calculated from the known bulk concentration using Eq. (1), confirming the role of the HLB binding gel as the infinite sink for the target pharmaceuticals. As shown in Fig. 4 and S13, the uptake masses of test pharmaceuticals on the HLB binding resin were inversely proportional to the diffusion layer thickness. Good agreement between the HLB-DGT measurements and the theoretical prediction line indicated the independence of accumulated mass on the diffusion layer thickness, which supported the validity of Eq. (1) to calculate CDGT.

3.6. DGT blanks and method detection limits

The IDLs, LOQs, DGT blank concentration and MDLs for the DGT and SPE methods of target pharmaceuticals are listed in Table S8. No target analytes were detected in the HLB-DGT blank units. The MDLs of DGT ranged from 0.01 to 6.51 ng L\(^{-1}\) for the deployment time of 1 day at 25 ± 0.2°C, which was similar to the MDLs of SPE (0.01–7.60 ng L\(^{-1}\)). The MDLs of DGT were much lower than most of the reported target pharmaceuticals concentrations in surface water for 1-d deployment (Huang et al., 2020), indicating that the MDLs of HLB-DGT provide sufficient sensitivity for environmental applications.

Fig. 3. Effects of flowing velocity of solutions on ratio of CDGT to Cb (IS = 0.01 M, pH = 6.5 ± 0.2 and T = 25 ± 0.2°C; n = 3). The error bars were calculated from the standard deviation of three replicates.

Fig. 4. Measured uptake masses (ng) of target pharmaceuticals in HLB-DGT devices deployed in well-stirred solution for different times and various diffusion layer thicknesses. The error bars were calculated from the standard deviation of three replicates.
### 3.7. Field applications

The applicability of HLB-DGT for monitoring target pharmaceuticals was evaluated in two urban rivers in Beijing, China. Due to the loss of seven HLB-DGT devices at the S4 site after deployment, only two DGT devices were collected. The water quality parameters of each sampling site during the DGT sampling period are given in Table S6. A comparison of TWA concentrations (7-day deployment) obtained by HLB-DGT and grab sampling at four sampling sites was presented in Fig. 5 and Fig. S14. Thirty target pharmaceuticals were detected in HLB-DGT or grab samples at all sites. The concentrations of the detected pharmaceuticals varied across a range from sub ng L\(^{-1}\) concentrations to hundreds of ng L\(^{-1}\).
L\(^{-1}\), which were generally comparable to the reported levels in major Chinese water bodies (Xiang et al., 2021). Three antiviral drugs used for COVID-19 treatment were detected in all sampling sites. The concentrations of ritonavir and lopinavir were much lower than those in the receiving rivers of Guangdong, China (Yao et al., 2021). The arbidol concentration levels were similar to that reported for the Khatoritsa River, Russia (Ul’yanovskii et al., 2022). Due to the poor removal efficiency of the three antiviral drugs in WWTPs (Ul’yanovskii et al., 2022; Yao et al., 2021), the manifold increase in their emission requires further investigation.

No significant difference (\(P > 0.05\), F-test, ANOVA) was found in the concentrations of the most detected pharmaceuticals between the two sampling methods. The results indicated that the TWA concentrations obtained by HLB-DGT were in accord with those obtained by grab sampling. As expected, the pharmaceutical concentrations at the S3 site were lower because of the greater dilution effect, whereas the other sampling sites showed relatively high concentrations as the locations near to the sewage outlet of the WWTPs. While the TWA concentrations obtained by the two sampling methods did not always coincide for CAP, CIP, LIN, and PEF. For example, as shown in Fig. 5, the CIP concentrations obtained by HLB-DGT at all sampling points except the S3 site were significantly higher than the detection limit, but it was not detected in all grab samples. PEF was detected by both sampling methods at the S2 and S3 sites but not detected by grab sampling at the other two sampling sites. This indicated that grab samples collected at an instantaneous time points are likely to miss the concentration fluctuations. The trace concentrations obtained by the HLB-DGT devices could be attributed to three HLB gels eluting together, reducing the detection limit (e.g. reducing a factor of 2.48 for CIP and 1.82 for CAP). The concentration of LIN obtained by the HLB-DGT devices was lower than the detected limit, which could be explained by the lower sampling rate due to the temperature effect (Fig. S14). Overall, the robust performance of HLB-DGT indicated that it is capable of measuring target pharmaceuticals in surface water.

No significant biofouling was observed in the HLB-DGT samples taken on the first, third, and seventh days (Fig. S1 (h), (i) and (j)). As shown in Fig. 6 and S15, the accumulated mass of target pharmaceuticals in HLB-DGT linearly increased with time, indicating that the HLB binding resin did not reach the saturated adsorption capacity for the 7-day sampling. It should be noted that SMM was detected only in the sixth and seventh days by HLB-DGT. The variation in the SMM sampling rate during the deployment period could be explained partly by inhomogeneous exposure (Schafer et al., 2008) and insufficient deployment time. For most target pharmaceuticals, there were no notable concentration fluctuations observed during the sampling period. The daily TWA concentrations obtained in the HLB-DGT devices were similar to those obtained by grab sampling (Fig. 6 and S15). The good response to daily concentration also illustrated the applicability of HLB-DGT in long-term monitoring of target pharmaceuticals.

4. Environmental implications

In this study, we expanded the variety of pharmaceuticals that can be detected by HLB-DGT, eight of which were reported for the first time.
Environmental concentrations of the three antiviral drugs used for COVID-19 treatment were detected in all sampling sites. Notably, these antiviral drugs have relatively high hydrophobicity (log Kow from 5.40 to 6.27, Table S1), which indicated that they have biological effects. Thus, strict control measures should be adopted to regulate their discharge in receiving water bodies.

Significant advantages of the DGT devices for monitoring organic pollutants were well-documented in previous studies (Chen et al., 2013; Fang et al., 2021; Zheng et al., 2015). Compared with grab sampling, target analytes preconcentrated in DGT devices reduced matrix interference and improved the accuracy of analytical testing. Compared to other passive sampling methods, DGT also has its disadvantage such as less sensitivity due to its low sampling rate. Therefore, longer deployment time is needed to meet the detection limit requirements. However, lower sensitivity issues can be compensated by enlarging the exposed area (Chen et al., 2020; Chen et al., 2013). Both Wei et al. (2019) and Uirk and Vrana (2019) had designed a symmetric structure, which meat two naked binding layer could simultaneously uptake and increase sampling rate. In the present study, three parallel HLB-DGT devices pooled as one sample to elute, which also achieve the same goal. As a result, the trace-level contamination of CAP was detected in HLB-DGT devices. Grab samples replicates may be limited in part by consideration of time, labor, and costs. Therefore, it is hard to provide representative time-integrative discrete samples by increasing the gaging sampling frequency (Challis et al., 2016). The comparable concentration between the two sampling methods indicated HLB-DGT was a cost-effective alternative to conventional grab sampling. However, fluctuation in pollutant concentrations are common in surface waters such as untreated sewer overflows (Mutzner et al., 2020) and extreme rainfall events (Corada-Fernández et al., 2017). Whether concentration fluctuations caused by episodic exposures and variable hydrodynamics can be captured by DGT devices should be further explored.

5. Conclusions

We developed the HLB-DGT sampling devices for monitoring 35 pharmaceuticals, including three antiviral drugs used for COVID-19 treatment, based on a comparative evaluation with XAD18 and XDA1 binding resins. HLB-DGT provided good performance for broad ranges of pH, IS, and flow velocity. Field applications validated the stability and reliability of HLB-DGT, which were comparable to the TWA concentrations obtained by the grab sampling. Therefore, the HLB-DGT devices can be used as an alternative to low-frequency grab sampling for monitoring pharmaceuticals. The reliable water quality monitoring information obtained by the HLB-DGT devices can help understand the overall implications of the occurrence and fate of pharmaceuticals in environmental waters. More work should extend the use of DGT to other organic pollutants requiring priority control. For fields monitoring in surface water, new configurations of DGT devices should be developed to address concern of low sampling rate not compensate by extending sampling time. It is possible to enlarge the exposure area or seek a promising substitution for the diffusive layer.

Author statement

Hongmei Cao: designed, planned, conceptualized, performed the analysis, drafted the original manuscript. Qingshan Li: funding acquisition, performed part of the experiments and data analysis. Xiaohong Gao: performed part of the experiments and sampling. Huaijun Xie: investigation, writing - review & editing. Wenwen Gong: investigation, writing - review & editing. Xiaoxiao Wang: performed part of the experiments and sampling. Lei Yang: investigation, writing - review & editing. Jianfeng Tang: resources, writing - review & editing.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.119979.

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