Internally-Calibrated Passive Samplers for Water Quality Assessment of Pharmaceuticals and Other Organic Compounds of Wastewater Origin

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Internally-Calibrated Passive Samplers for Water Quality Assessment of Pharmaceuticals and Other Organic Compounds of Wastewater Origin

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Introduction

Assessments of the fate, and ultimate biological and human exposures, of pharmaceuticals and other organic compounds that originate from municipal or agricultural wastewater discharges are limited by the expense of sample analyses. Many municipal wastewater treatment plants in Connecticut discharge to small streams and rivers such that treated wastewater constitutes a significant fraction (10 – 30 %) of total flow. Nationwide, fractional contributions of greater than 10 percent treated effluent in river systems are characteristic of about one quarter of the discharge points under average flow conditions and up to two thirds under low flow conditions (*e.g.* 7Q10) (Brooks *et al.*, 2006). Pharmaceuticals and other compounds of wastewater origin are of concern because of their potential biological activity, including endocrine disruption; however, few studies have documented their subsequent degradation rates or phase transfer processes following release to aquatic systems. Most environmental reports of pharmaceuticals and other organic compounds of wastewater origin are point observations obtained through grab samples. More detailed evaluations of compound loss mechanisms require multi-observation time series that are not feasible given the $200-$800 price per sample for compound analyses. Thus, there is a need to develop robust, yet cost-effective, sampling methodologies that provide insights into the environmental system dynamics of pharmaceuticals and other organic compounds of wastewater origin.

Passive samplers offer an alternative to grab samples that overcome some of the limitations of grab samples, including detection limits, episodic concentration changes and cost for long time-series sampling (Morin *et al.*, 2012). Passive samplers are deployed for an extended period of time (days to weeks) to take up analytes of interest from the contacting water. Mass uptake in the sampler is quantified through a less-labor intensive extraction step than utilized in conventional grab samples. The mass uptake (M, ng) is then converted to an effective aqueous concentration by normalizing to a compound-specific mass uptake rate (k, L h^{-1}) multiplied by the deployment time (t, h), yielding a time-weighted average concentration (C_w, ng L^{-1}):

$$C_w = M \cdot k^{-1} \cdot t^{-1} \quad (1)$$

Time-averaged concentrations are considered more representative of endpoint biological exposures than point observations of CWO concentrations (Morin *et al.*, 2012). Passive sampler deployment can also improve upon detection limits, thereby reducing costs associated with analyzing samples that ultimately are below the detection limit. A larger sample mass uptake can be obtained through a longer deployment period than for a single 500 – 1000 mL water sample. Monitoring of time-weighted concentrations smooths episodic changes in CWO concentrations that could result in missing 'peaks' with grab sampling (Morin *et al.*, 2012).

The most widely applied passive samplers for CWO are Polar Organic Compound Integrative Samplers (POCIS) developed by Alvarez *et al* (2004). POCIS contain a layer of high-polarity sorbent resin (as used for conventional water extraction) sandwiched between two membrane filters (Fig. 1 (a)). The specialized resin allows for the uptake of very polar and/or charged CWO; however, the mass uptake rates must be derived empirically from extensive laboratory calibrations that are compound-specific and quite sensitive to flow conditions (Fig. 1(a)).

Jones and collaborators recently proposed an alternative to the POCIS sampler design that integrates a fundamental parameter (diffusion coefficient) into the mass uptake rate (Chen *et al.*, 2012). The thin film diffusive gradient (DGT) passive sampler for CWO contains a layer of high polarity sorbent resin overlaid with a porous gel layer (Fig. 1(b)). Because the limiting mass transfer step is diffusion across the porous gel layer (Fig. 1(b)), the mass uptake rate is constant for a particular compound:

$$k_{DGT} = D_{DGT} \cdot A \cdot \Delta x^{-1} \cdot 10^{-3} \quad (2)$$

where D_{DGT} ($cm^2\ h^{-1}$) is the compound-specific diffusion coefficient in the gel layer, A (cm^2) is the exposed area of the sampler, Δx (cm) is the thickness of the gel layer, and 10^{-3} ($L\ cm^3$) is a unit conversion. As a result, the DGT sampler design has very low sensitivity to variations in flow conditions during deployment (Chen *et al.*, 2013). Importantly, compound-specific D_{DGT} values for a large suite of CWO can be derived from a small number of experimentally measured values by applying a molecular weight scaling model (Zhang and Davison, 1999):

$$D_{DGT} = 3\times10^{-5} \cdot \Theta^2 \cdot MW^{-1/3} \quad (3)$$

where Θ is the gel porosity, MW is the compound molecular weight. Initial field deployments showed good agreement between DGT estimates of time-weighted CWO concentrations in water samples and observations from 24-hour composite sampling (Chen *et al.*, 2013).

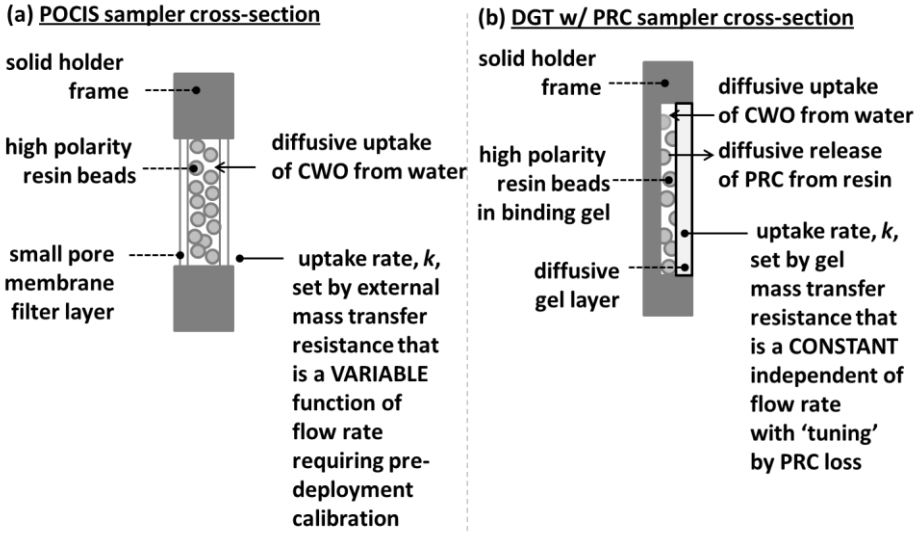

Figure 1. Schematic cross-section profiles of passive samplers noting the location of limiting mass transfer steps and the consequent influence on the sampler uptake rate, *k*, that is critical to calculating time-averaged aqueous concentrations (Eq. 1). Sampler length 5-8 cm.

Re

The objective of this project is to develop a passive sampling device that will provide an integrated assessment of pharmaceuticals and other compounds of wastewater origin in water bodies so that low concentration samples can be quantified with lesser effective expense. Specific tasks to develop such a sampling device include:

i. Assess the use of internal standards to calibrate for flow variations across sampling device deployments.

ii. Evaluate the sensitivity of sampling devices to temporal variations in input mass fluxes of compounds.

iii. Measure environmental loss rates of compounds in streams receiving modest inputs of treated municipal wastewater.

At the time of report preparation, progress has only been made toward completion of Task (i). Other tasks will be completed during summer 2016.

Methods

Experiments were performed to characterize the components of the DGT sampler by measuring diffusion coefficients in the agarose material from which the gel layer was cast and binding coefficients for the sorbent resin. Target compounds were chosen to be complementary to parallel NSF-funded research examining photodegradation of pharmaceutical compounds, downstream of wastewater discharge locations (Bodhipaksha *et al.* 2016). Compounds are commonly observed in treated municipal wastewater discharges and each has a unique degradation mechanism when exposed to sunlight – sulfamethoxazole (SMX) and sulfadimethoxine (SDM) both degrade by direct photolysis, cimetidine (CMT) reacts with sunlight-produced singlet oxygen, and caffeine (CAF) reacts with sunlight-produced hydroxyl radicals. Additionally, these compounds all exhibited different speciation characteristics under the circumneutral pH conditions expected for many river systems. Sulfamethoxazole and sulfadimethoxine are both zwitterionic compounds with both positive and negative charge, cimetidine is positively charged and caffeine is neutral.

Chemicals. Sulfamethoxazole, sulfadimethoxine, caffeine and cimetidine (all ≥99% purity) were purchased from Sigma-Aldrich (US). Agarose powder (3:1) was obtained from Nusieve. Acetonitrile (HPLC grade) was from Acros Organics. High purity water (18 MΩ-cm) was used for all experiments and obtained from a Milli-Q system (Waters). HLB Max anion exchange resin was obtained from Waters.

Gel preparation. Agarose gel was prepared by adding an appropriate mass of agarose power to pre-heated high purity water to a final concentration of 1.5 % agarose by weight. The solution was mixed in a boiling water bath until the solution was clear. The solution was then poured onto a glass plate. Spacers of thickness 0.5 mm were placed on the corners of the glass plate and the gel mixture was compressed to 0.5 mm thickness by placing a second glass plate overtop of the spacers. The gel was allowed to firm and then stored in a high purity water bath to keep it hydrated and to avoid any tearing.

Diffusion cell. A diffusion cell was used to measure the transport of compounds through the gel material. The diffusion cell consisted of two glass reservoirs that contacted opposite sides of a holder containing a sample of the gel (Fig. 1). The effective diameter of the gel material contacting the two sides was 1.5 cm. A circular piece of agarose gel was cut from a gel sheet using a custom-designed punch. The gel section was then placed in a holder that was clamped between the two reservoirs. One of the reservoirs was filled with 100 mL of solution containing a 1×10^{-4}

M concentration of the compound of interest. The other reservoir was filled with 100 mL of high purity water. Solutions were adjusted to a pH of 7 ± 0.3 and held at room temperature (22 ± 2 °C). The system was held in darkness to avoid compound photodegradation. Subsamples were collected every 3 hours for a period of 3 to 5 days, depending on time to equilibrium.

Analysis. Pharmaceutical compound concentrations were quantified using high performance liquid chromatography (HPLC) (HP 1050, Agilent) with a C_{18} reverse phase column (Licosphere) and an acetonitrile (30%)-water (70%) eluent. Compounds were detected at a wavelength of 225 nm and concentrations were quantified with an external calibration curve.

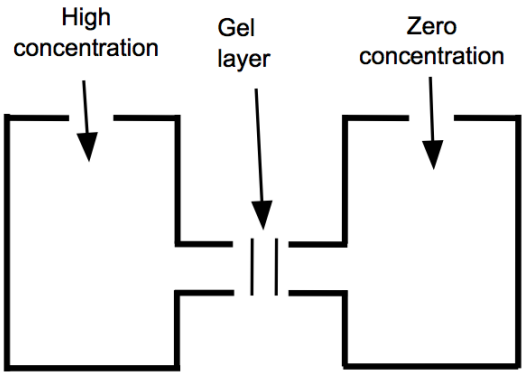

Fig. 1 Diagram of diffusion cell used to obtain data for compound diffusion through the agarose gel material. Compounds moved from left to right in response to a diffusion gradient from high concentration (1×10^{-4} M) to zero concentration (high purity water).

Diffusion coefficient calculations. Diffusion coefficients for compound transport across the agarose gel were obtained by fitting compound concentrations as a function of time (Crank, 1956):

$$C(t) = C(\infty) + \big(C(0) - C(\infty)\big)e^{\left(-\frac{D*A*t}{V*\Delta g}\right)} \quad (1)$$

where C (M) is the concentration on the 'high concentration' side as defined in Fig. 1, C(∞) (M) is the concentration at equilibrium (equal to one half of the initial concentration), C(0) (M) is the initial concentration at time zero, D (cm^2/s) is the diffusion coefficient, A (cm^2) is the exposed gel area between the two reservoirs, t (s) is the elapsed time at subsample collection, V (cm^3) is the volume of the 'zero concentration' reservoir as defined by Fig. 1m and Δg (cm) is the thickness of gel layer.

Sorbent Resin Binding. Compound sorption to HLB Max resin was quantified using a column chromatography method (Jolin *et al.* 2016) with a high performance chromatography system. A small dimension (30-mm length, 2.1-mm diameter, Restek) column was packed with a mixture of resin and the inert solid silicon carbide. A second column was packed with silicon carbide to confirm that compounds had no interactions with this material. Uracil was used as a non-interacting tracer to measure transport times through the column system. Flow of a 5 mM $CaCl_2$ solution (to mimic river background ionic strength) was initiated at a rate of 100 µL/min.

Results and Discussion

Diffusion Coefficients. The mass transport of the neutral compound, caffeine, across the agar gel was first examined for comparison to previously published results. Experimental runs were monitored seven days until equilibrium was reached between both of the reservoirs, as evaluated by final concentrations in both of the reservoirs being half of the starting concentration in the initial 'high concentration' reservoir (Fig. 1). The resultant diffusion coefficient was 1.5 ×

10^{-5} cm^2/s and similar to a previously observed value of 4×10^{-5} cm^2/s for caffeine diffusion through agar gel (McCabe 1972). A lower measured than reported caffeine diffusion coefficient could indicate that the gel layer was somewhat thicker than the targeted thickness of 0.5 mm from the spacers used herein, or because caffeine interacts with the agarose gel material as it diffuses through the gel layer. The latter explanation was excluded after conducting batch sorption experiments in which the concentration of caffeine in a solution was contacted with pieces of agarose gel material in well-mixed test tubes and found not to change over a four-day period.

The reproducibility of the gel casting method was evaluated by examining the sulfamethoxazole diffusion across gel material subsamples. First, differences in gel thickness across the same cast were examined by comparing data for SMX-1 and SMX-2 in Fig. 2. Although the trends in concentration with time look similar between the two trials, fits of the data with Eq. 1 indicated the diffusion coefficients to vary by 30% (Tab. 1). These differences indicate variations in the thickness of the gel layers, as a constant value of Δg was assumed in calculating the diffusion coefficients. A second gel cast (SMX-3) showed the range of diffusion coefficients to be similar between replicate gel sheets (Fig. 2, Tab. 1). Together these results highlight the importance of a performance reference compound to be incorporated into the sampler to account for differences in gel layer thickness between subsamples that may be up to 30 percent.

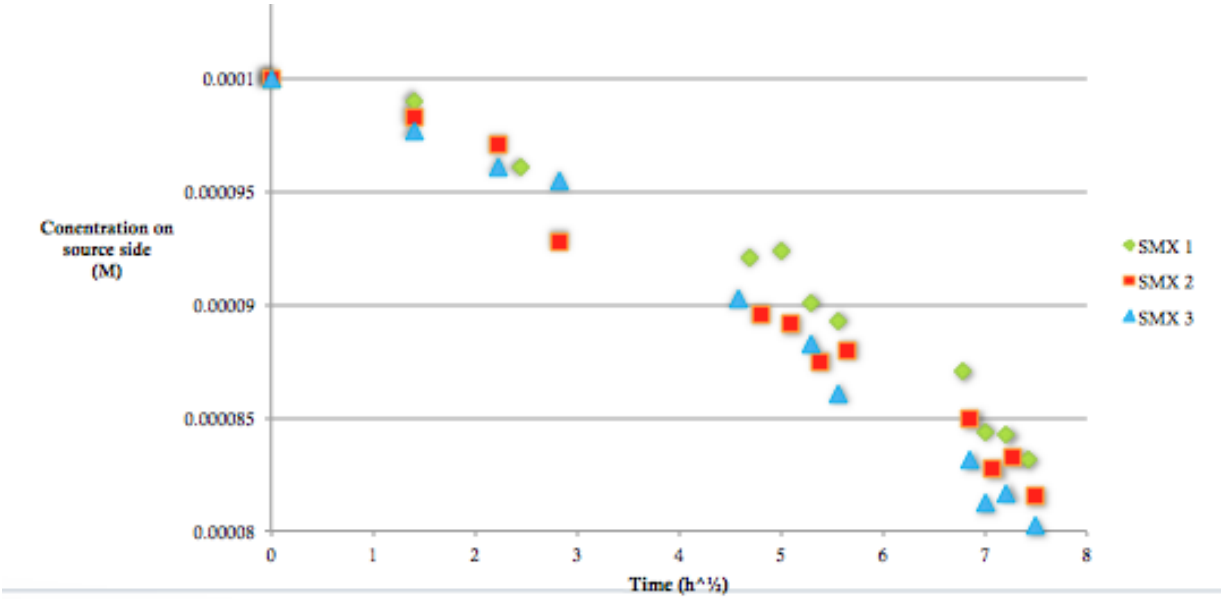

Fig. 2. Sulfamethoxazole transport from the 'high concentration' reservoir for duplicate subsamples of a single gel sheet (SMX-1 green diamonds, SMX-2 red squares) and from a duplicate gel sheet (SMX-3).

Tab. 1. Compound diffusion coefficients obtained by fitting Eq. 1 to the changing compound concentrations in the 'high concentration' reservoir (Fig. 1) over time.

Compound	**MIxture**	**Diffusion Coefficient (cm^2/s)**
Sulfamethoxazole	No	SMX-1: 3.4×10^{-5} SMX-2: 4.5×10^{-5} SMX-3: 4.9×10^{-5}
	Yes	3.6×10^{-5}
Cimetidine	No	4.9×10^{-5}
	Yes	7.0×10^{-5}
Sulfadimethoxine	Yes	4.1×10^{-5}

The presence of multiple compounds was also confirmed to have no effect on the diffusion of a single compound through the gel layer. The change in cimetidine concentration over time showed little effect from the presence of the other compounds (CMT Mix, Fig. 3), compared to cimetidine alone (CMT, Fig. 3). Fitted diffusion coefficients were within the variation observed for replicate gel sections (Tab. 1). Overall, diffusion coefficients through the

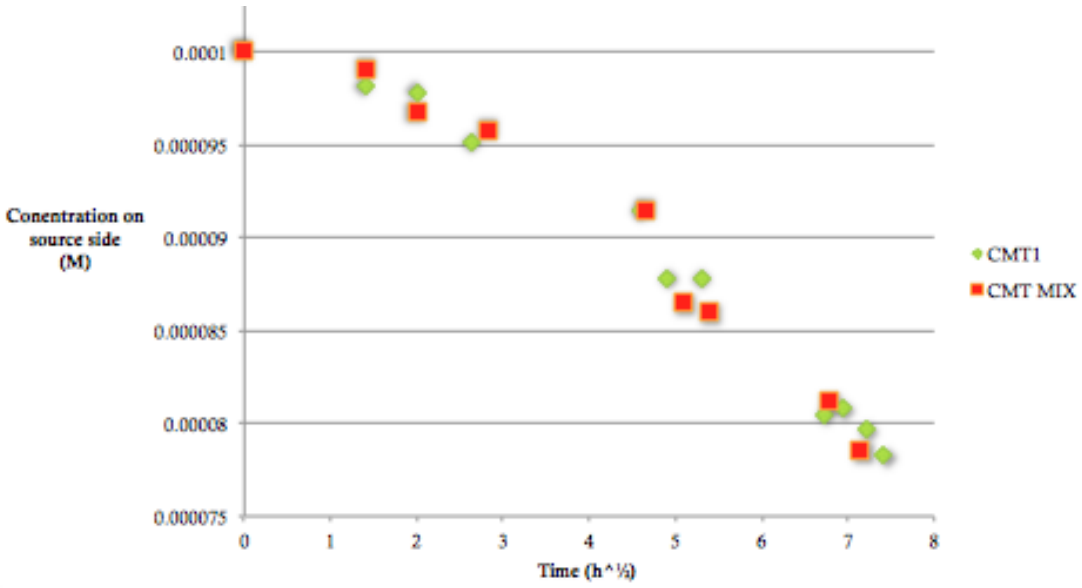

Fig. 3. Comparison of concentration changes for cimetidine diffusion through the gel media as a single solute (green diamonds) and in the presence of a mixture of cimetidine, sulfamethoxazole, sulfadimethoxine, all present initially at 1×10^{-4} M (red squares).

Column Chromatography to Measure Compound Binding to Sorbent Resin. Initial evaluations were performed to assess whether column chromatography can be used as a high throughput approach for measuring binding coefficients of compounds to HLB Max anion exchange resin. First, silicon carbide was determined to be an inert diluent for mixing with sorbent resin beads. The retention time of sulfamethoxazole transport through a column packed with silicon carbide was only slightly greater than for the compound uracil which is known not to interact with sorbent media (Tab. 2). Sulfamethoxazole was retained on a column containing HBL Max anion exchange resin, compared to uracil.

Tab. 2. Compound retention times on chromatography columns.

Column	Compound	Time to center of peak
Silicon Carbide	Uracil	2.24
Silicon Carbide	Sulfamethoxazole	2.91
HLB Max resin	Uracil	2.37
HLB Max resin	Sulfamethoxazole	11.25

Work is continuing to replicate results in Tab. 2 and to obtain retention times for the other compounds of interest so that their binding to sorbent resin is well-characterized before sampler construction.

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