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Aqueous Solubility, *n*-Octanol–Water Partition Coefficient, and Sorption of Five Selective Serotonin Reuptake Inhibitors to Sediments and Soils

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Abstract Aqueous solubilities (S_w) and *n*-octanol–water partition coefficients (K_{ow}) of five selective serotonin reuptake inhibitors (SSRIs) were measured and sorption to two sediments and three soils with organic matter contents ranging from 0.16% to 1.77% and pH ranging between 5.0 and 7.8 was investigated using a batch equilibrium method. SSRIs had high S_w (3,022–15,460 mg/l) and relatively low log K_{ow} (1.12–1.39). Sorption isotherms followed the Freundlich equation. All SSRIs had sorption capacities of greater than 91% except fluvoxamine with a minimum capacity of 73%. Organic matter contents partly affected sorption, however no correlation between sorption characteristics and cation exchange capacity (CEC) or clay content was observed for any SSRI or adsorbent. Values of K_f, K_d, and log K_{oc} ranged from 39 to 18,342, from 60 to 42,579, and 3.35 to 6.02 for the SSRIs. SSRIs likely exhibit mixed mechanisms of sorption such as ionic binding in addition to hydrophobic interactions.

Keywords Water solubility · Octanol–water partition coefficients · Sorption · Selective serotonin reuptake inhibitor

Data from the European Union has shown that many pharmaceuticals are commonly detected in surface waters receiving sewage treatment plant effluent (Daughton and Ternes 1999). Although very low concentrations of drugs are typically detected in aquatic systems, chronic usage of drugs ensure a constant, low-level exposure regime for aquatic organisms living in water (Daughton and Ternes 1999). Numerous papers have shown the occurrence of pharmaceuticals in the environment such as ground water (Eckel et al. 1993; Holm et al. 1995; Stan et al. 1994; Stan and Linkerhägner 1992), lake and ocean (Buser and Müller 1998), surface water and wastewater (Buser et al. 1998, 1999), and sediment (Coyne et al. 1994; Kerry et al. 1995). Recently many classes of pharmaceuticals, hormones, and other organic wastewater contaminants including some selective serotonin reuptake inhibitors were also detected in US streams (Kolpin et al. 2002). Recent other papers have reported detections of selective serotonin reuptake inhibitors (SSRIs) except fluvoxamine in water (Lamas et al. 2004; Metcalfe et al. 2003; Weigel et al. 2004).

Only one abstract and one published paper indicate that fluoxetine was detected in water, sediment, wastewater-irrigated soil, and biosolid products (Furlong et al. 2004) and in soils irrigated with reclaimed water (Kinney et al. 2006). Selective serotonin reuptake inhibitors are a class of drugs that are prescribed for the treatment of clinical depression in humans and are some of the most heavily prescribed drugs in the USA. In a survey performed by NDCHealth in 2004, many of the SSRIs were within the top 200 prescriptions for 2004 by number of US prescriptions dispensed (http://www.rxlist.com/top200.htm) indicating there is a huge potential for detecting SSRIs and their metabolites/degradation products in the aquatic environment. However, little data currently exist on their environmental fate including sorption characteristics to sediments and soils.

The solubility of a chemical in water and its hydrophobicity are crucial parameters and are needed for other environmental fate and ecotoxicological assessment,

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however sorption to soils or sediments of a chemical is also an important factor.

The objectives of this investigation were to determine aqueous solubility (S_w) and *n*-octanol–water partition coefficient (K_{ow}), and to evaluate the sorption behaviour of five SSRIs (citalopram HBr, fluoxetine HCl, fluvoxamine maleate, paroxetine HCl, sertraline HCl) to two sediments and three soils with different physico-chemical properties.

Materials and Methods

Figure 1 shows the molecular structures of five selective serotonin reuptake inhibitors. Fluoxetine hydrochloride and fluvoxamine maleate standards were purchased from Sigma-Aldrich (St. Louis, MO, USA) and sertraline hydrochloride and paroxetine hydrochloride standards from Toronto Research Chemicals Inc. (North York, Ontario, Canada). Only citalopram hydrobromide standard could not obtain commercially, thus citalopram hydrobromide was extracted with ethanol from Celexa® (Forest Pharmaceuticals, Inc. St. Louis, MI, USA) and purified by recrystalization with diethyl ether. The purity and identity of purified citalopram was confirmed by high performance liquid chromatography (HPLC) and liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS). For the purity determination, the purified citalopram solution was injected on to an HPLC and the chromatographic response was monitored at 210 nm. The purity of the purified citalopram was more than 99%. The mass spectrum of citalopram showed the same patterns as published data (Müller et al. 2000). All solvents were HPLC grade and were obtained from Fisher Scientific (Fair Lawn, NJ, USA). Calcium chloride from J.T Baker (Phillipsburg, NY, USA) was used to prepare electrolyte solution and 0.01 M calcium chloride solution was prepared in distilled water.

Aqueous solubility was measured in unbuffered distilled-deionized water by the flask saturation method (Eirkson et al. 1987). The temperature of the laboratory was maintained at 22°C. A predetermined excess quantity (40 mg) of drugs was added to a 15-mL polyethylene centrifuge tube (Fisherland, Pittsburgh, PA, USA) containing 1.5 mL of water. These solutions were shaken for 36 h and centrifuged at 5,400 g for 20 min followed by careful transfer of the supernatant to a glass tube. Samples were then diluted 100- or 1,000-fold in water before analysis, followed by assay for each drug by HPLC. This experiment was run in triplicate.

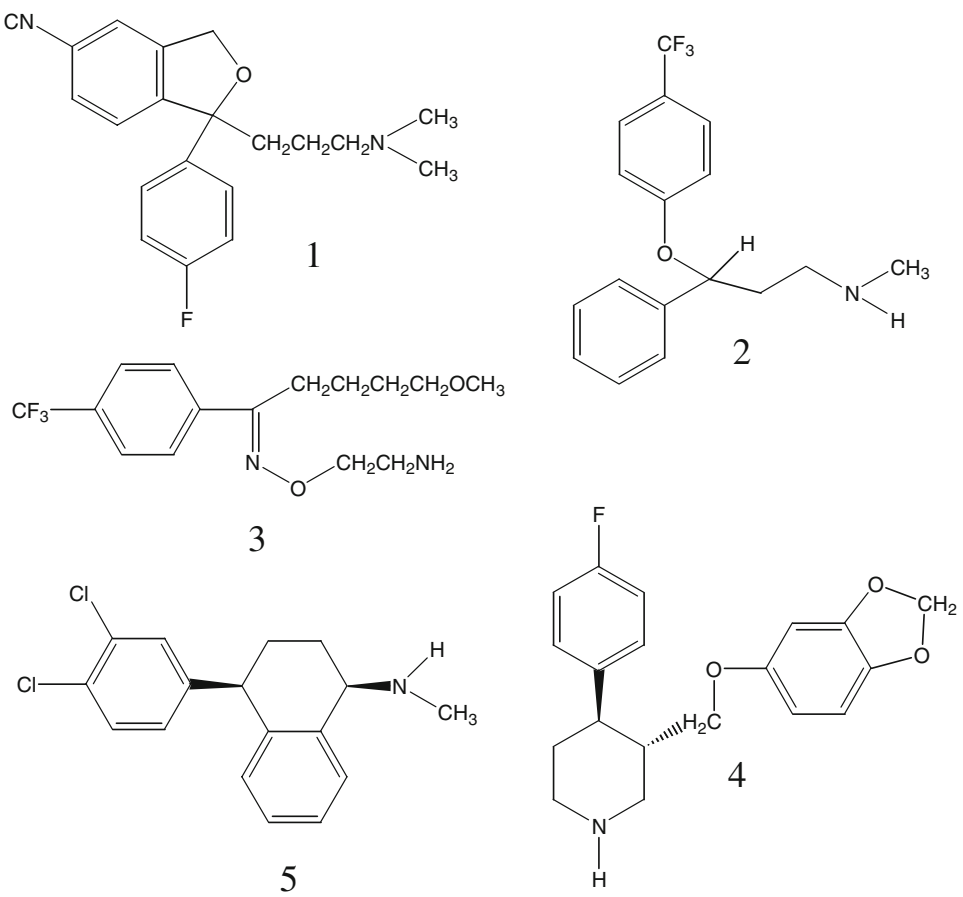

Fig. 1 Molecular structures of citalopram (1), fluoxetine (2), fluvoxamine (3), paroxetine (4), and sertraline (5)

n-Octanol–water partition coefficient values were determined using the shake-flask method (US EPA 1982). *n*-Octanol saturated with water was used as the organic phase, and water saturated with *n*-octanol was used as aqueous phase. *n*-Octanol solutions of each drug of two different known concentrations (0.5 and 2.5 mM) were prepared. An aliquot of 3 mL of these solutions was added to a 50-mL of polyethylene centrifuge tube (Fisherland, Pittsburgh, PA, USA) containing 30 mL water saturated with *n*-octanol. The tubes were shaken for 5 h at 22°C and centrifuged at 4,600 g for 20 min. The concentration of drugs in the aqueous phase was determined by HPLC after appropriate dilution with water. *n*-Octanol–water partition coefficient values were calculated by dividing the concentration in M of the drug in the organic phase by that in the aqueous phase. This experiment was run in triplicate.

Two sediments were collected from the top 0–20 cm of a creek (Sediment 1, Eupora, MS, USA) and a pond (Sediment 2, Mississippi State, MS, USA) and three soils were taken from surface horizons (0–20 cm) from two agricultural fields (Soil 1, Stoneville, MS, USA; Soils 2 and 3, Mississippi State, MS, USA). Samples were air-dried and passed through 2-mm sieve. The physico-chemical properties of the sediments and soils were analyzed in the Soil Testing Laboratory in the Mississippi State University and are summarized in Table 1. The clay in soils and sediments was composed of montmorillonite.

The standard stock solutions of five SSRIs were made up in deionized water at a concentration of 1,000 mg L^{-1}. Aqueous solutions of each SSRI were prepared in 0.01 M calcium chloride solution at final concentrations of 0.5, 1, 2, 5, and 10 mg L^{-1}. The batch sorption experiments were carried out in 50-ml polypropylene centrifuge tubes containing 2.5 g of sediments or soils and 25 ml of $CaCl_2$ solution containing each SSRI. Prior to starting the main experiments, two additional tests with a sample with sediment but without drug and a sample with drug but without sediment were conducted to evaluate interference by sediment and sorption onto the tube surface, respectively. These experiments indicated that interference and sorption were negligible. Additional preliminary tests indicated biotic degradation of SSRIs in sediment or soil slurries was negligible during the experimental period. Therefore, any observed mass lost from the supernatant in sediment or soil slurries was assumed to be sorbed by the sediment/soil. The centrifuge tubes were capped and shaken in a wrist-action shaker (Pittsburgh, PA, USA) for each equilibrium time. Preliminary tests indicated that the equilibrium times were 1, 3, 3, 2, 1.5 h for citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, respectively. At the end of equilibrium time, the suspension was centrifuged at 4,500 rpm for 20 min. The target analytes in the supernatants were analyzed using HPLC. For each solution, the amount of SSRI remaining was calculated as a percentage of concentration prior to shaking (zero time). All tests were conducted in triplicate. Sorption data were fit to the logarithmic form of the Freundlich equation:

$$\log C_s = \log K_f + 1/n \log C_e \quad (1)$$

where C_s is the concentration of drug sorbed to sediment (μg g^{-1}), K_f is the Freundlich sorption coefficient, 1/n is the slope of the sorption isotherm, C_e is the equilibrium concentration (μg mL^{-1}). The distribution coefficient, K_d, is represented as the amount sorbed divided by final equilibrium concentration. K_{om} is also represented as follows (Patakioutas and Albanis 2002):

$$K_{om} = 100 \times K_f/(\%OM) \quad (2)$$

Generally it is accepted that K_{om} equals $1.724 \times K_{oc}$ (Lyman et al. 1990) so the following was used to calculate K_{oc} as follows:

$$K_{oc} = K_{om}/1.724 \quad (3)$$

The amount of SSRIs remaining in solution was measured by direct injection of the aqueous sample onto a Waters 2695 HPLC with UV detection using a Waters (Model 996, Milford, MA, USA) photodiode-array detector. When analytes were not detected due to low concentrations, methylene chloride was used to extract SSRIs from the aqueous phase and the extract concentrated under nitrogen. Recoveries ranged from 92% to 96% for all SSRIs. Data were processed using MassLynx (Ver 3.4) software (Waters). A Waters Nova-Pak® C18 (3.9 × 150 mm)

Table 1 Physico-chemical properties of two sediments and three soils used

Adsorbent	Texture	Clay %	Silt %	Sand %	Organic matter %	pH	CEC[a] Meq 100 g^{-1}
Sediment 1	Silt	0.00	92.75	7.25	0.16	6.7	0.90
Sediment 2	Silt loam	7.50	66.25	26.25	0.65	5.6	7.73
Soil 1	Loamy sand	6.25	7.50	86.25	1.01	5.0	10.30
Soil 2	Sandy loam	7.50	16.75	75.75	1.77	7.8	72.49
Soil 3	Loamy sand	5.00	8.50	86.50	0.93	7.8	34.97

[a] Cation exchange capacity

analytical column was used for chromatographic separation and the mobile phase used was composed of acetonitrile (A)-distilled water containing 10 mM aqueous triethylamine (B), with the pH adjusted to 4.8 by addition of 85% phosphoric acid. Isocratic mobile phases of A/B (v/v) were as follows: 42/58 for citalopram and fluvoxamine; 45/55 for fluoxetine and sertraline; 50/50 for paroxetine. The flow rate was 1.0 mL min^{-1}.

Results and Discussion

As can be seen in Table 2, all SSRIs had relatively high S_w (3,022–15,460 mg L^{-1}) and relatively low log K_{ow} (1.12–1.39) values, and the relative standard deviations of the determined S_w and K_{ow} were reasonably low. All SSRIs did not degrade in the *n*-octanol stability test and also were stable in aqueous solutions as reported in prior published works (Kwon and Armbrust 2004, 2005a,b). It is likely that low K_{ow} values are due to high aqueous solubilities. Values of log K_{ow} were not dependent on the concentrations (0.5 and 2.5 mM) of the SSRIs in the water, suggesting that no dissociation or association occurred. The only published paper (Cunningham et al. 2004) reported S_w and log K_{ow} of paroxetine with 6,804 mg L^{-1} in distilled-deionized water (pH 6.5) and 1.30–1.35 in pH 7 buffer, respectively. Fluvoxamine includes the functional group $-NH_2$. For this SSRI, the log K_{ow} value is smaller than others, possibly because it easily forms hydrogen bonds between the nitrogen moiety in this molecule and the water molecules in the aqueous phase. Compared to that of fluvoxamine, the log K_{ow} value of sertraline is larger, probably due to the inclusion of hydrophobic functional groups such as –Cl and $-CH_3$.

All SSRIs in each soil sludge reached sorption equilibrium within 3 h. The sorption isotherms of the five SSRIs are shown in Figs. 2–6 (Panels A). The equilibrium sorption could be depicted by the Freundlich sorption isotherm as shown in Eq. 1 (Panels B). All SSRIs showed sorption capacities of greater than 91% except fluvoxamine with minimum of 73%, indicating high sorption capacity. Citalopram had the highest sorption at greater than 99%. A high correlation coefficient ($r^2 > 0.99$) in all cases

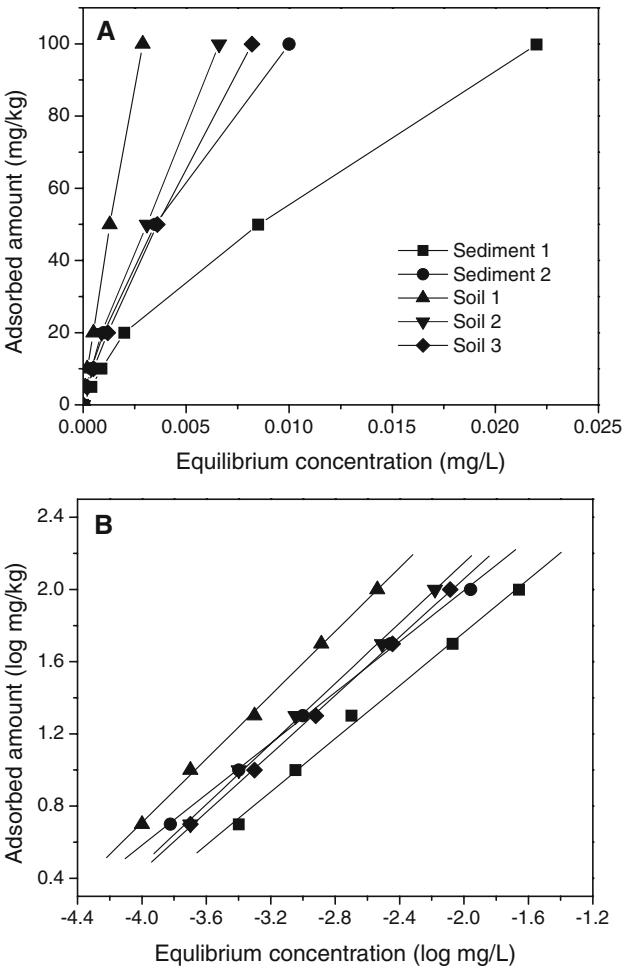

Fig. 2 Sorption of citalopram to sediments and soils

indicates that the Freundlich isotherm fit the behaviour as shown in Figs. 2–6 (Panels B). The slope of the sorption isotherm, 1/n, if equals to 1, indicates non-linearity in the sorption isotherm (Corwin and Farmer 1984). Most isotherms were non-linear with slopes of <1 (0.61–0.96) with the exception of sertraline (0.81–1.07) (Table 3).

According to the classification made by Giles et al. (1960), the sorption of citalopram, fluvoxamine, and sertraline is described by L-shaped isotherms for all soils and sediments (Figs. 2A, 4A, and 6A), indicating decreased sorption sites as the solution concentration increases. The

Table 2 Water solubilities and *n*-octanol–water partititon coefficients (log K_{ow}) of five SSRIs[a] (n = 3)

SSRI	Water solubility (mg L^{-1}, avg ± SD[b])	log K_{ow} (avg ± SD[b])
Citalopram	15460 ± 220	1.39 ± 0.1
Fluoxetine	10762 ± 159	1.22 ± 0.1
Fluvoxamine	14869 ± 293	1.12 ± 0.1
Paroxetine	6213 ± 95	1.37 ± 0.0
Sertraline	3022 ± 31	1.37 ± 0.1

[a] All values represents average ± standard deviation (n = 3)

[b] Average ± standard deviation (SD)

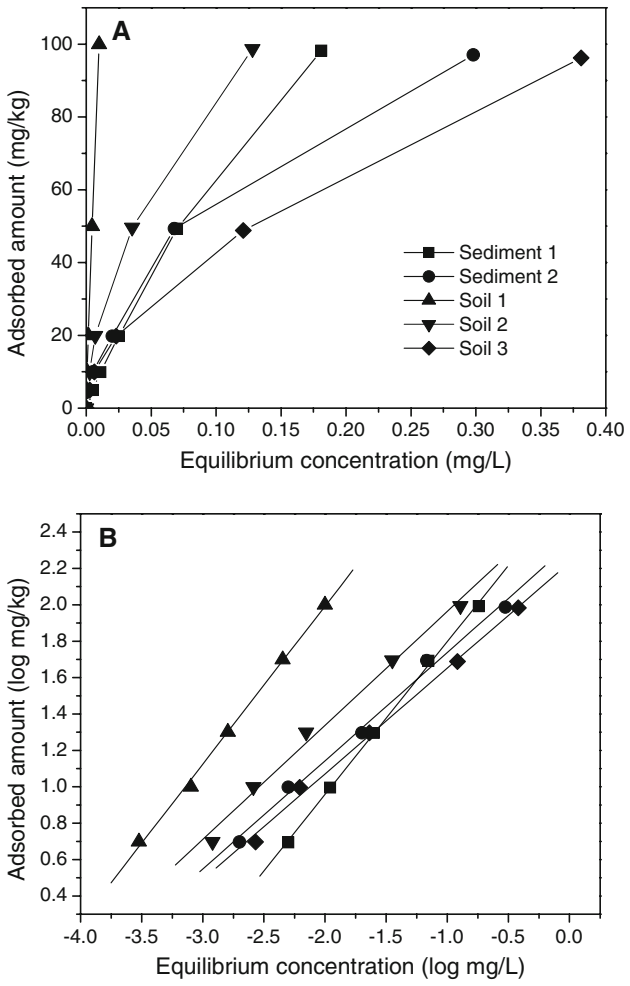

Fig. 3 Sorption of fluoxetine to sediments and soils

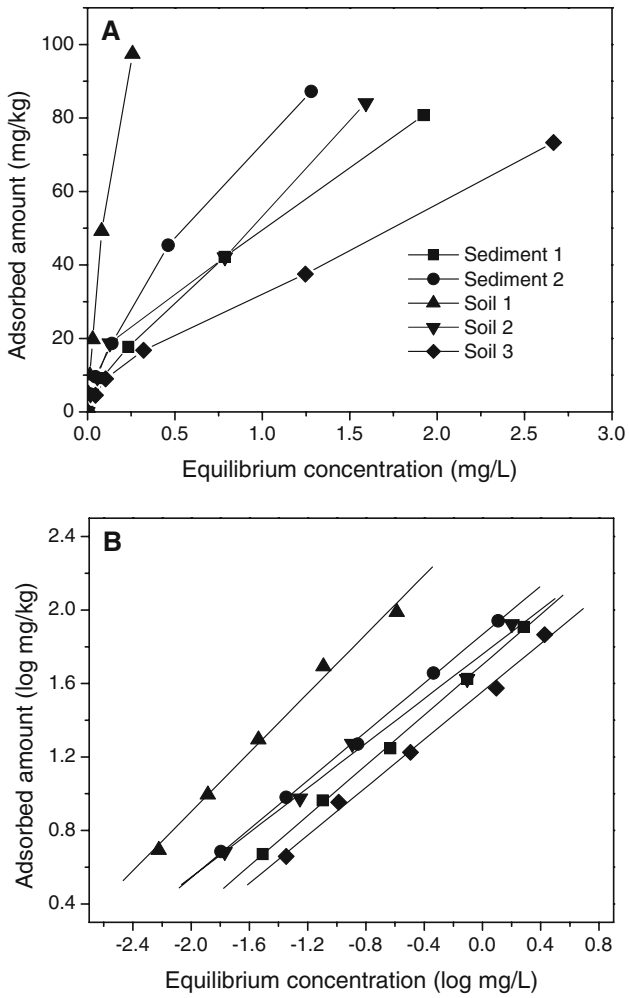

Fig. 4 Sorption of fluvoxamine to sediments and soils

L-isotherm is the best known, especially L2 curve, which occurs in the majority of cases of sorption of organic chemicals from dilute solution (Giles et al. 1960). This type of isotherm suggests that these compounds are most likely to be sorbed rapidly in a flat position on the adsorbents and do not compete for sorptive sites on soil surfaces (Giles et al. 1960; Calvet 1989; Patakioustas and Albanis 2002). The sorption of fluoxetine and paroxetine were also described by L-shaped isotherms in four adsorbents including sediments 1 and 2 and soils 2 and 3. However, the isotherm for fluoxetine and paroxetine was characterized as a C-shaped isotherm in soil 1, which had the lowest pH (5.0). Giles et al. (1960) suggested that this C-type isotherm is a linear curve and corresponds to a constant partitioning of the solute between the bulk solution and adsorbent particles, especially the organic matter fraction.

Freundlich constants K_f and 1/n, distribution coefficient K_d, log K_{om}, and log K_{oc} for the sorption of five SSRIs are given in Table 2. Values of K_f, K_d, and log K_{oc} ranged from 39 to 332, from 60 to 649, and 3.35 to 6.02, respectively, indicating very high sorption coefficients. The US EPA classifies log K_{oc} values "very strong" (>>4.5), "strong" (3.5–4.5), "moderate" (2.5–3.4), "low" (1.5–2.4), and "negligible" (<1.5) (US EPA 2003), suggesting that all the SSRIs had more than "strong" sorption capacity, even "very strong", except for fluvoxamine in soil 2 and 3 (these values, 3.35 and 3.38, are also pretty close to 3.5). No statistical correlation between sorption characteristics and CEC or clay content was found for any SSRI and adsorbent characteristics. It was found that, in general, pH is the only factor influencing sorption of SSRIs. However, pH is always not a factor determining the degree of sorption. The highest values of K_f and K_d were found in soil 1 with the lowest pH (5.0) in each SSRI, indicating the highest capacities of sorption. The highest sorption in soil 1 could not be explained by any other adsorbent characteristics. SSRIs with the lowest K_f values for each adsorbent except citalopram are due possibly to the highest pH of 7.8. Although soil 2 has the highest pH (7.8), it had the second highest K_f values except for fluvoxamine, probably due to the high organic matter contents, suggesting that organic

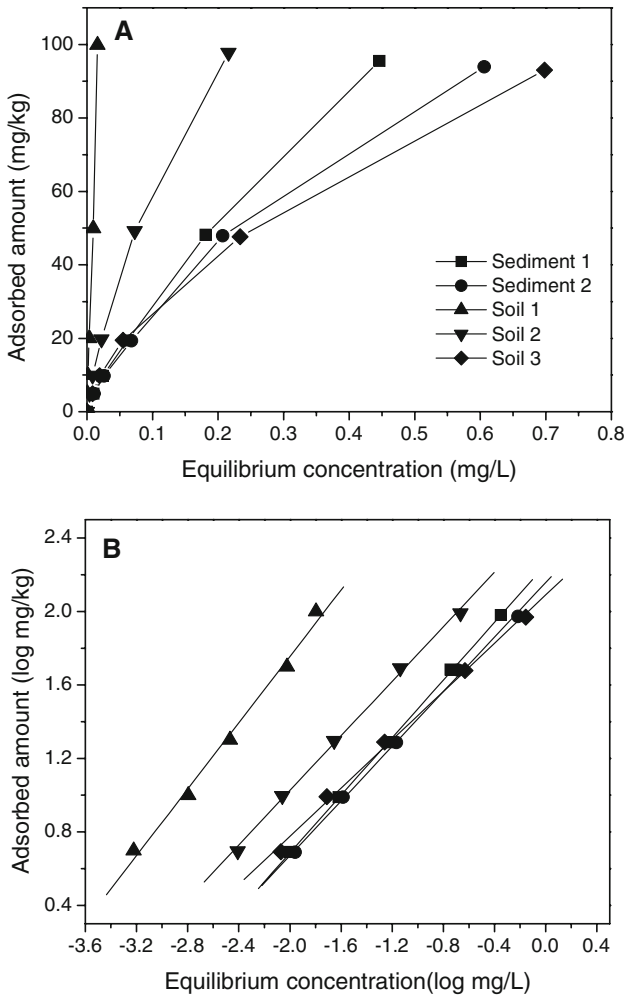

Fig. 5 Sorption of paroxetine to sediments and soils

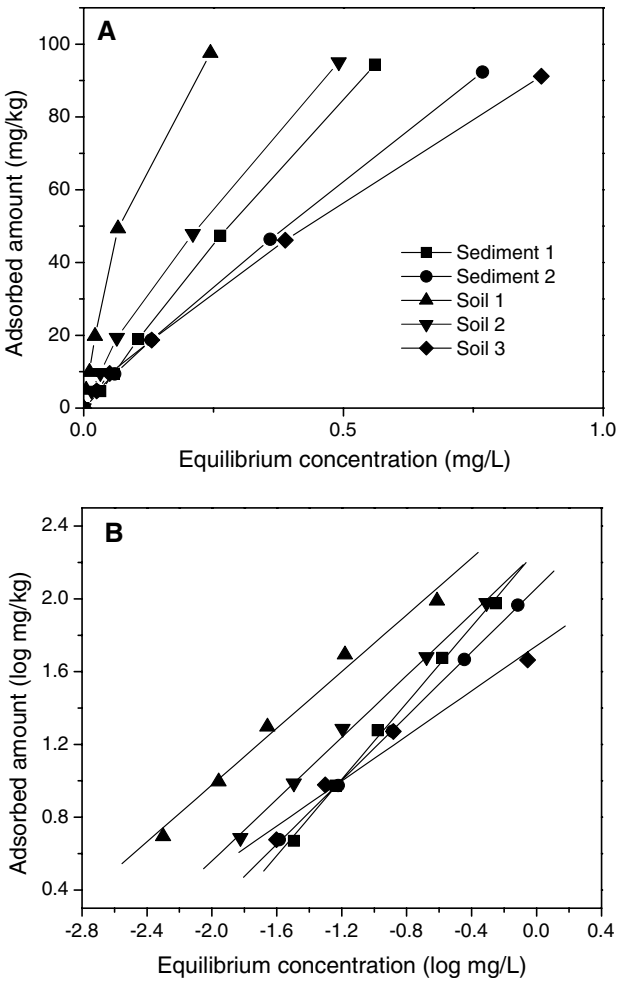

Fig. 6 Sorption of sertraline to sediments and soils

matter content of soils and sediments partly influences sorption of SSRIs. Kinney et al. (2006) have also reported that soil organic matter may, in part, play a role in the greater retention of several pharmaceuticals including fluoxetine in soil. Simple linear regressions between selected adsorbent properties (clay content, organic matter content, CEC, pH) and the Freundlich constant, K_f, were calculated and indicated that sorption is generally correlated with the pH ($r = 0.42$–0.73). Others are as follows: clay content, $r = 0.03$–0.38; organic matter content, $r = 0.12$–0.48; CEC, $r = 0.13$–0.27. Kinney et al. (2006) have reported that although having high water solubility (12,900 mg/L) (Chen et al. 2002), high pK_a (9.4–9.5) (Dasmalchi et al. 1995; Kulkarni and Pegram 2000), and low log K_{ow} (Snyder et al. 2003), acetaminophen accumulated in soil as much as other pharmaceuticals (erythromycin, carbamazepine, and fluoxetine) with low water solubility less than 100 mg L^{-1} and relatively high log K_{ow} did. Like acetaminophen, all the SSRIs had high water solubility (3,022–15,460 mg/L), high pK_a (9.39–10.32) (Vasskog et al. 2006), and low log K_{ow} (1.12–1.39). So it is likely that SSRIs may similarly behave in view of soil accumulation to acetaminophen.

As all of the SSRIs are organic bases with pK_a values typically >9 (citalopram, pKa = 9.59; fluoxetine, pKa = 10.05; fluvoxamine, pKa = 9.39; paroxetine, pKa = 10.32; sertraline, pKa = 9.47) (Vosskog et al. 2006), each SSRI will be cationically charged at environmentally relevant pH values. This explains both the strong sorption (combination of ionic binding + organic carbon partition) and high S_w and low log K_{ow} (they are ionized). Therefore, it is likely multiple mechanisms may be important explaining the high sorption capacity.

It is known that sorption mechanism for neutral and hydrophobic compounds may be related to the organic carbon content of biomass, soils, or sediments and thus reasonably well correlated with the K_{ow}, and ionizable compounds may exhibit mixed mechanisms of sorption, such as cation exchange, cation bridging at clay surfaces, surface complexation, and hydrogen bonding other than

Table 3 Freundlich constants K_f and 1/n, distribution coefficient K_d, log K_{om}, and log K_{oc} for the sorption of five SSRIs (n = 3)

SSRI	Adsorbent	1/n	K_f	K_d	log K_{om}	log K_{oc}
Citalopram	Sediment 1	0.77	2,103	8,798	6.1	5.88
	Sediment 2	0.70	2,362	18,666	5.6	5.32
	Soil 1	0.89	18,342	42,579	6.3	6.02
	Soil 2	0.88	8,938	20,691	5.7	5.47
	Soil 3	0.81	4,794	17,540	5.7	5.48
Fluoxetine	Sediment 1	0.83	419	785	5.4	5.18
	Sediment 2	0.61	229	1,304	4.6	4.31
	Soil 1	0.87	5,429	12,546	5.7	5.49
	Soil 2	0.67	480	2,602	4.4	4.20
	Soil 3	0.62	198	992	4.3	4.09
Fluvoxamine	Sediment 1	0.69	51	88	4.5	4.26
	Sediment 2	0.66	73	163	4.1	3.82
	Soil 1	0.81	332	649	4.5	4.28
	Soil 2	0.70	69	141	3.6	3.35
	Soil 3	0.71	39	60	3.6	3.38
Paroxetine	Sediment 1	0.78	178	338	5.1	4.81
	Sediment 2	0.74	143	298	4.3	4.11
	Soil 1	0.96	5,067	6,386	5.7	5.46
	Soil 2	0.75	334	886	4.3	4.04
	Soil 3	0.68	131	355	4.2	3.91
Sertraline	Sediment 1	1.07	194	168	5.1	4.85
	Sediment 2	0.88	115	147	4.3	4.01
	Soil 1	0.81	396	787	4.6	4.36
	Soil 2	0.87	191	270	4.0	3.80
	Soil 3	0.84	106	149	4.1	3.82

hydrophobic interactions (Tolls 2001; Cunningham et al. 2004). Therefore, for these compounds, K_{ow} values may not properly predict their fates in soils or sediments. That is, prediction of log K_{oc} by log K_{ow} may lead to significant underestimation of log K_{oc} (Tolls 2001).

In conclusion, all SSRIs had high S_w (3,022–15,460 mg L^{-1}) and relatively low log K_{ow} (1.12–1.39) values. Different kinds of soils or sediments have different sorption capacity for SSRIs. In general, all the SSRIs had high sorption coefficients. The sorption capacity on soil 2 (pH, 5.0) is the largest, while that of soil 3 (pH, 7.8) is the smallest, which is negatively correlated with pH of soil and sediment for all SSRIs. These data also indicated that organic matter contents partly positively affect sorption of SSRIs to soils and sediments although cation exchange mechanisms are also likely since these are organic bases and will be cationically charges at environmentally relevant pH values. Among SSRIs tested, citalopram had the highest sorption parameter values. From our unpublished data, citalopram showed the highest detection frequency and detection levels in downstream sediment samples, which corresponds to sorption results.

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