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Temporal and spatial behavior of pharmaceuticals in Narragansett Bay, Rhode Island, United States

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Abstract

The behavior and fate of pharmaceutical ingredients in coastal marine ecosystems is not well understood. To address this, the spatial and temporal distribution of 15 high volume pharmaceuticals were measured over a one year period in Narragansett Bay, RI, USA to elucidate factors and processes regulating their concentration and distribution. Dissolved concentrations ranged from ND to 313 ng/L, with 4 pharmaceuticals present at all sites and sampling periods. Eight pharmaceuticals were present in suspended particulate material, ranging in concentration from ND to 44 ng/g. Partitioning coefficients (K_ds) were determined for some pharmaceuticals, with their range and variability remaining relatively constant throughout the study. Normalization to organic carbon content (K_{oc}) provided no benefit, indicating other factors played a greater role in regulating partitioning behavior. Within the upper Bay, the continuous influx of wastewater treatment plant (WWTP) effluents resulted in sustained, elevated levels of pharmaceuticals. A pharmaceutical concentration gradient was apparent from this zone to the mouth of the Bay. For most of the pharmaceuticals, there was a strong relationship with salinity, indicating conservative behavior within the estuary. Short flushing times in Narragansett Bay coupled with pharmaceuticals' presence overwhelmingly in the dissolved phase indicates that most pharmaceuticals will be diluted and transported out of the estuary, with only trace amounts of several compounds sequestered in sediments. The present study identifies factors controlling the temporal and spatial dynamics of dissolved and particulate pharmaceuticals; their partitioning behavior provides an increased understanding of their fate, including bioavailability in an urban estuary.

Keywords

Pharmaceutical; Environmental partitioning; Contaminants; Wastewater; Estuarine

INTRODUCTION

The long-term sustained release of pharmaceuticals into natural waters worldwide has become a growing concern as both the number and volume of prescription and non-

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prescription drugs consumed increases [1]. Many of these pharmaceutical ingredients can be classified as contaminants of emerging concern, with their potential ecological effects and those of their metabolites poorly understood [2]. To date, freshwater systems (e.g., rivers and lakes) have been more frequently examined and better characterized for potential effects from pharmaceuticals than have coastal waters and estuaries [3,4], despite high population density and growth in coastal areas globally [5].

Direct releases of pharmaceuticals to the estuarine environment result from discharge of wastewater treatment plant (WWTP) effluents [3,6]; however, riverine inputs from coastal watersheds are also important since they receive effluents from WWTPs [7,8]. The removal efficiencies of pharmaceuticals during wastewater treatment are highly variable, differing among compound classes and the level and type of treatment [9,10]. Combined with high prescription rates and sustained usage of many pharmaceuticals, the potential for elevated, steady-state concentrations in receiving waters exists [11,12]. Exposure to these compounds, which are likely still bioactive in the dissolved phase of the water column, has the potential to cause adverse effects. Further, mixtures of many pharmaceuticals have the potential for additive or synergistic interactions, elevating the risk of toxicity to aquatic organisms [1,2]. Risk of potential pharmaceutical bioaccumulation or adverse ecological effects maybe especially a concern for near-shore coastal areas where benthic and littoral marine organisms are commercially harvested and farmed for human consumption.

Estuaries are extremely dynamic and complex ecosystems, with each having unique physical, chemical and biological attributes. The magnitude of WWTP discharges are an important factor [13] regulating the quantities of pharmaceuticals present in estuarine receiving waters. These discharges combined with hydrodynamic processes such as tides and circulation patterns play key roles in the transport, dilution and distribution of pharmaceuticals, ultimately controlling their concentration and residence time in estuaries [14].

Water column variables such as salinity and pH, as well as suspended particulate matter (SPM), can vary greatly over short time and spatial scales, potentially affecting the speciation, sorption and partitioning of pharmaceuticals in marine waters [15]. Many pharmaceuticals are polar and ionic, with their sorption properties and partitioning behavior in estuarine waters not well understood [16]. Some pharmaceuticals, especially those that are cationic [17,18], can be sorbed by partitioning to SPM and removed from the water column. A key aspect of the present study was to examine the spatial and temporal variability of pharmaceuticals and determine the extent that they partition between the dissolved and suspended particulate phases in the estuarine environment. The long term measurement of pharmaceuticals provides essential information to better understand conditions influencing their behavior and supports improved predictions of their exposure, effects, and ultimately, if needed, their regulation [19].

In the present study we investigated 15 highly consumed pharmaceuticals comprising 8 classes: 6 antihypertensives, 2 antibiotics, 2 diuretics, an antilipemic, an anticonvulsant, an analgesic, an antiulcerative, and a stimulant. These pharmaceuticals were selected based on their high prescription rate in the US, and their high frequency of occurrence in wastewater

effluents and freshwater systems at elevated levels [4]. The compounds were measured over a one-year period (2014–2015), 11 times in the dissolved phase and 4 times in the suspended particulate phase at 8 sites located throughout Narragansett Bay, an urbanized estuary highly impacted by WWTP discharges. The objectives were to assess factors controlling their spatial and temporal concentrations and investigate their partitioning behavior and variability in order to characterize their fate and bioavailability in estuarine systems.

MATERIALS AND METHODS

Study Area

Narragansett Bay is located on the northeast coast of the United States between the states of Rhode Island and Massachusetts and has a warm summer continental climate with a watershed area of 4081 km^2 and a population of 1.8 million people [20] (Figure 1). Classified as a coastal plain estuary, the Bay has an area of 342 km^2, an average depth of 9 m, and a volume of 2.7×10^9 m^3 at mid tide [21] (Figure 1). Narragansett Bay's tides are semidiurnal with a range of 1.1 to 1.4 meters and are the primary drivers of circulation. The mouth of the Bay has two distinct openings, the east and west passages (with the east passage being significantly deeper than the west), and both are connected to Rhode Island Sound. Most of the coastline of Narragansett Bay is densely populated, with all large communities connected to WWTP facilities. In Narragansett Bay, rivers account for up to 80% percent of its freshwater inputs, with WWTP discharge to these rivers being a significant contributor to total river flow. Most of the freshwater comes from three river systems: the Blackstone which discharges to the Seekonk and Providence Rivers, the Taunton, and Pawtuxet Rivers (average flows 9.07×10^6 m^3/d), all of which are characterized as urban rivers which have large-scale inputs from WWTPs [21]. Total daily effluent discharges to these rivers is estimated at 7.6×10^5 m^3/d or approximately 8% of total river flow. Flushing time for Narragansett Bay has been calculated at 26.5 days for average freshwater flow (9.07×10^6 m^3/d) with a range of 10 to 40 days using the tidal prism method, which utilizes both fresh and saltwater inputs to the estuary [22,23].

Eight sites within Narragansett Bay were selected for water and SPM sampling based on their proximity to WWTPs, freshwater inputs, and major physical and bathymetric features (Figure 1). Three sites—Fields Point, Pawtuxet Cove, and Nyatt Point—are located within the Providence River sub-embayment, which receives the greatest volume of wastewater discharge and freshwater river flow (Supplemental Data, Table S1). Two sites, Greenwich Bay and Mount Hope Bay, are located on the west and east sides of the middle of Narragansett Bay, respectively. The last 3 sites are located in the lower Bay in close proximity to Rhode Island Sound, which is the source of ocean water to the Bay. The Newport site is in the east passage, the Bay Campus site is in the west passage at the University of Rhode Island, and the Jamestown site is positioned just north of Conanicut Island, which separates the east and west passages. Site features along with their distances from local WWTPs are in Supplemental Data, Table S2.

Sampling

Water samples were collected from 1 m below the water surface at each site 11 times over the course of one year at approximately one month intervals (Supplemental Data, Table S3). Water was pumped through a Teflon coated pump, through a 1 μm spiral wound glass fiber filter and stored in amber glass bottles. Samples were kept on ice until returned to the laboratory, and stored in the dark at 4°C. Suspended particulate matter was collected by sediment traps deployed 4 times during the study period. Deployment and recovery of the traps occurred during the week in morning hours on days that water was collected. Deployment periods ranged from 49 to 62 days in order for sufficient SPM to settle into the traps for analysis. One exception was the December deployment which averaged over 100 days due to freeze over of the Bay. Several traps separated from their bottom anchors during study and were not recoverable (Supplemental Data, Table S3). After retrieval, the sediment traps were decanted of overlying water and the particulate contents were freeze-dried.

Water extractions

Extraction protocols followed EPA Method 1694 with slight modifications [19], using Oasis HLB solid phase extraction (SPE) cartridges (6 cc, 500 mg, Waters Corporation). For the acidic extractions, 500 mL samples were adjusted to pH 2 using hydrochloric acid (6N) and spiked with 100 ng of isotopically labeled pharmaceuticals (Supplemental Data, Table S4). Cartridges were conditioned with 6 mL of methanol, followed by 6 mL of Milli-Q water, 6 mL of pH 2 Milli-Q, and 6 mL of pH 2 filtered artificial seawater. Samples were loaded onto SPEs using a vacuum manifold at a rate of 5–10 mL/min. After loading, the SPEs were rinsed with 12 mL pH 2 Milli-Q water, dried for 15 minutes under vacuum and eluted with 12 mL of methanol. Extracts were then evaporated to dryness, reconstituted with 500 μL mobile phase (Milli-Q:methanol,80:20), vortexed, transferred to vials and stored at 4°C until analysis. The basic extraction was conducted in the same manner; however, for conditioning and sample loading pH levels were adjusted to pH 10 using ammonium hydroxide (30% as NH_3), and the SPE elution step consisted of 6 mL of methanol followed by 6 mL methanol containing 2% formic acid. A blank, fortified blank, duplicate, and matrix evaluation were included in each set of extractions.

Sediment extractions

For extractions of pharmaceuticals from SPM, a modified version [19] of the QuEChERS extraction procedure [24] was utilized. Briefly, 5 g of homogenized freeze-dried SPM were weighed into a 50-mL centrifuge tube and 10 mL of acetonitrile acidified with 100 μL of acetic acid, 1.5 g of acetate buffer and 3 g $MgSO_4$ were added. The mixture was shaken manually and subsequently vortexed for 1 minute. The samples were loaded onto a wrist action shaker and agitated for 1.5 hours, then centrifuged at 2500 rpm for 15 minutes and decanted. Afterwards, a 1 mL aliquot of the acetonitrile phase was transferred by pipette and passed through a 0.45 μm filter, evaporated to dryness and reconstituted in 500 μL mobile phase. Recoveries of SPM spiked with 100 ng of the reported pharmaceuticals resulted in recoveries ranging from 94 to 127%.

Analysis

The 15 pharmaceuticals in the present study were antihypertensives (atenolol, metoprolol, propranolol, verapamil, valsartan, and diltiazem), antibiotics (sulfamethoxazole and trimethoprim), diuretics (hydrochlorothiazide and furosemide), an antilipemic (gemfibrozil), an anticonvulsant (carbamazepine), an analgesic (acetaminophen), an antiulcerative (ranitidine), and a stimulant (caffeine) (Table 1). The pharmaceuticals were quantified using high purity standards (Sigma Aldrich-Fluka) with isotopically enriched surrogates (deuterated and/or ^{13}C) as internal standards (CDN Isotope) (Supplemental Data, Table S5). Compounds were separated into three groups to optimize their extraction and analysis conditions (Supplemental Data, Table S6). Analysis was performed on a Waters Acquity UPLC using a Waters Xevo TQD MS/MS operated in electrospray ionization (ESI) mode. Compounds were detected by MS/MS with ionization conditions of the source set to 0.5 kV in ESI+ and 3.5 kV in ESI- (Supplemental Data, Table S7). Compound specific settings were also used for quantification and confirmation multiple reaction monitoring (MRM) transitions in the appropriate mobile phase (Supplemental Data, Tables S4, S6). Compounds were calibrated using a 10 point curve ranging from 0.25 ng/mL to 300 ng/mL. Calibration curves consistently had an $r^2 = 0.99$ or better for all pharmaceuticals. Calibration verification standards were also analyzed every 10 samples to confirm instrumental performance over the course of the analytical run. Recoveries were generally within 10% of documented values throughout the course of the study for each pharmaceutical. Method detection limits were determined for each of the pharmaceuticals using instrument detection limits defined as S/N>10 and are reported in Supplemental Data, Table S6 for water and sediment. Further information on quality assurance is provided in Supplemental Data, Table S8.

RESULTS

Effluent and riverine inputs

During this study, major river inputs to Narragansett Bay averaged 52 m^3/s (range 5–300 m^3/s) based on USGS river gage data [25]. Three rivers—the Blackstone (including the Seekonk and Providence), Taunton and Pawtuxet—accounted for ~80% of the freshwater flow to Narragansett Bay in 2015 [25]. This resulted in a long-term daily average riverine input of 8.2×10^5 m^3/d to Narragansett Bay. There are 33 WWTPs within the Narragansett Bay Watershed that discharge directly to the Bay or to rivers and streams that drain to the Bay (Supplemental Data, Table S1). Most of the WWTP effluent discharged (~70%) occurs in the northern part of the bay within the Providence River (Figure 1) [26]. Approximately 23% enters the bay through the Taunton River or by direct discharge into Mount Hope Bay. The balance of effluent enters the mid to lower Bay locations primarily from ~8 small WWTPs. The location and magnitude of WWTP outfalls and riverine inputs along with tides, circulation patterns and hydrologic features within the Bay result in a strong north-south (high-low) gradient of effluent discharge.

Dissolved pharmaceuticals

The dissolved concentrations of all pharmaceuticals are presented in Figure 2 and Supplemental Data, Table S9. Four of the 15 pharmaceuticals investigated (metoprolol, atenolol, valsartan and caffeine) were measurable at all sites and sampling periods,

demonstrating their widespread distribution in the Bay. Three of these pharmaceuticals are highly prescribed antihypertensive drugs, while caffeine is present in numerous compounded pharmaceuticals and abundant at high levels in many beverages and foods. Six other pharmaceuticals—carbamazepine, sulfamethoxazole, trimethoprim, diltiazem, gemfibrozil and hydrochlorothiazide—appeared less frequently, present from 50 to 93% of the time during the study. Finally, 5 pharmaceuticals—acetaminophen, propranolol, ranitidine, verapamil and furosemide—were limited in their presence over time and space, relegated primarily to locations in the upper Bay, which is in close proximity to high volume WWTP and riverine inputs. With the exception of caffeine, acetaminophen, and furosemide, all of the pharmaceuticals displayed a north to south concentration gradient.

Metoprolol had the highest levels of all pharmaceuticals in the study, ranging from 1.1 to 313 ng/L. The highest levels were at the Providence River sites (Fields Point, Pawtuxet Cove and Nyatt Point), showing several spikes in concentration during warmer months. Atenolol behaved similarly, but at lower concentrations. Valsartan had some of the highest overall pharmaceutical levels measured throughout the study. Concentrations of caffeine were also on the higher end, but in a spatial context relative to other pharmaceuticals, a north-south gradient with distance from WWTP sources and river inputs in the upper Bay did not exist.

The highest concentrations of the 6 other most frequently present pharmaceuticals were all recorded at the Pawtuxet Cove and Fields Point sites, and were also present occasionally at all other sites. Frequency of occurrence at these 2 sites was high as well, with all occurring 100% of the time, excepting hydrochlorothiazide at 91%. Levels of carbamazepine ranged from below detection to 63 ng/L across sites. Sulfamethoxazole and trimethoprim remained below 20 ng/L, with the exception of sulfamethoxazole in Pawtuxet Cove at 47 ng/L. Both had 100% frequencies of occurrence at the upper 3 stations, while sites in the lower Bay had generally lower occurrence rates and concentrations. Diltiazem was present at most sampling intervals, remaining below 10 ng/L, showing slightly higher levels from November through March. Gemfibrozil was present for much of the study (77%), ranging from non-detect to more than 70 ng/L. Hydrochlorothiazide was consistently present at the 2 northernmost sites, with levels in Pawtuxet Cove exceeding 277 ng/L, followed by Fields Point at 81 ng/L. In the lower Bay, levels ranged from non-detect to 75 ng/L.

Concentrations of acetaminophen remained below 15 ng/L throughout the Bay, with the exception of Greenwich Bay which had a single elevated value of 60 ng/L in March 2015. Verapamil remained below 3 ng/L throughout the study, and was absent at three sites (Mount Hope Bay, Newport and Bay Campus). In contrast, in Pawtuxet Cove it was measurable at 6 of the sampling intervals and at the highest levels recorded in the Bay. Ranitidine and propranolol were measurable only at the three sites within the Providence River, with an occurrence rate of just 18% and 22%, respectively. Concentrations of both remained below 15 ng/L. Finally, furosemide was detected only 3 times during the study, ranging from 4 to 45 ng/L.

Particulate pharmaceuticals

Of the 15 pharmaceuticals investigated, 8 were measurable in the particulate phase and at relatively low levels, indicating minimal affinity for sorption under estuarine conditions

(Figure 3; Supplemental Data, Table S10). Of these, caffeine, metoprolol and verapamil had the highest occurrence in SPM. Sediment traps from several sites were lost during the study, limiting the temporal interpretation of the SPM data (Supplemental Data, Table S3). The number of pharmaceuticals present at each site declined as distance from the Providence River increased (e.g., Pawtuxet Cove 8; Fields Point 7; Nyatt Point 5; Mount Hope Bay 4; North Jamestown, Bay Campus, Greenwich Bay 2; Newport 1). The most ubiquitous pharmaceutical in the SPM samples was caffeine. Other pharmaceuticals present at sites in declining order were metoprolol (6); verapamil (5); carbamazepine, propranolol, and trimethoprim (3); atenolol (2); and ranitidine (1). Metoprolol had the highest overall levels at 44 ng/g, followed by verapamil and atenolol with 14 and 13 ng/g, respectively. The other pharmaceuticals that were present were below 10 ng/g.

DISCUSSION

Spatial trends

In Narragansett Bay there was a clear spatial trend for most of the dissolved pharmaceuticals along a well-defined north-south concentration gradient. Stations in the upper Providence River (i.e., Pawtuxet Cove, Fields Point and Nyatt Point) consistently had the highest concentrations with declining levels at stations in the lower Bay (Figure 2). The Pawtuxet Cove site generally had the highest overall levels of most pharmaceuticals due to the proximity of the Pawtuxet River. The Pawtuxet River receives effluent from 3 WWTPs with a combined average daily effluent flow of 8.1×10^4 m^3/d [24], which at times accounts for more than 1/3 of total river flow [27]. Dilution at this site is relatively limited, influencing the levels observed (Figure 2; Supplemental Data, Table S9). The Fields Point site is within 1 km of a major WWTP outfall which discharges on average 1.7×10^5 m^3/d of secondary treated effluent (Supplemental Data, Table S1). Other freshwater inputs to the upper Providence River average 1.7×10^6 m^3/d, mostly from the Blackstone River, which also has significant loadings of WWTP effluents (Supplemental Data, Table S1).

Combined, WWTPs account for more than 5.7×10^5 m^3/d of effluent discharged daily to a small convergence zone within the upper Providence River. Within this area, a condition of steady-state input exists with concentrations of pharmaceuticals remaining at elevated levels. The sustained levels observed here over time for most of the pharmaceuticals occurred despite relatively short flushing times of approximately 3 days [22]. It is in these zones [28] where potential adverse effects from pharmaceuticals are most likely to be a concern based on the elevated concentrations consistently measured at these locations (Figure 2; Supplemental Data, Table S9). The sustained, elevated concentrations of pharmaceuticals is evidence of the impact that WWTP discharge magnitude and proximity has on this small area of the upper Bay. Slightly south is the Nyatt Point site near the mouth of the Providence River, which has the lowest pharmaceutical levels of the 3 river sites. Here, pharmaceutical concentrations were lower as mixing and dilution occurred during transport down-river and as Bay-wide hydrodynamic processes started to become a factor.

In the mid Bay are two sites located in sub-embayments, Greenwich Bay and Mount Hope Bay (Figure 1), which are semi enclosed and influenced to a lesser extent by local WWTP discharges than the upper Bay (Supplemental Data, Table S1). Both locations have discrete

features that distinguish them from other locations. Greenwich Bay is unique in that it receives submarine groundwater inputs that are suspected to include residuals from residential septic treatment systems [29] and would likely include pharmaceuticals. In Mount Hope Bay, considerable fresh water enters from the Taunton River, which has 6 small WWTPs in its urban watershed contributing 1.1×10^5 m^3/d of effluent daily. In addition, the Fall River WWTP discharges 7.8×10^4 m^3/d in the vicinity (~ 3.4 km) of our sampling site (Supplemental Data, Table S1). During wet weather events, combined sewage overflow (CSO) discharges in Fall River episodically occur (~ 3.2×10^6 m^3/yr), releasing untreated wastewater to this sub-embayment. Both sites have lower levels of pharmaceuticals than those in the Providence River, due to reduced wastewater loadings and receiving waters with greater area. Both Greenwich Bay [30] and Mount Hope Bay [31] have approximate flushing times of 3.3 and 2 days respectively, which also influences the levels of pharmaceuticals observed. The elevated levels of dissolved caffeine at both these sites relative to locations in upper Providence River may be explained by contributions from untreated wastewater sources such as CSOs and submarine groundwater inputs, which have been identified as potential sources to these sub-embayments.

The 3 remaining sites—Newport, North Jamestown and Bay Campus—are situated close to Rhode Island Sound and generally had the lowest concentrations and most non-detects of all sites. This is due to several factors, which include low effluent discharge volume in the area (Supplemental Data, Table S1) and circulation patterns in the east and west passages involving large volumes of water continuously moving out of the Bay into Rhode Island Sound [23], providing rapid flushing and transfer of dissolved pharmaceuticals from Narragansett Bay to open oceanic water.

The observed decline in the presence and abundance of pharmaceuticals from the Upper Providence River to the mouth of Narragansett Bay is a pattern that has been identified for other pollutants. Previous research in Narragansett Bay has established a similar spatial gradient between water column concentrations of nutrients—specifically nitrogen, which is a significant component of domestic WWTP effluents [32]. In Narragansett Bay, there is a well-defined, year round salinity gradient that displays a negative correlation with nutrients [33], which may also be the case for pharmaceuticals. This salinity gradient is driven by the large volume of freshwater inputs into the Upper Bay (i.e., Providence River), physical processes (e.g., tides and circulation patterns) and the morphology of the estuary.

To assess whether dissolved pharmaceuticals in Narragansett Bay were acting conservatively, compound-salinity mixing curves were developed for pharmaceuticals (Figure 4). The pharmaceuticals verapamil, furosemide, ranitidine, propranolol and acetaminophen are not presented as their presence was limited across time and space, particularly at lower Bay sites. The mean dissolved pharmaceutical concentrations versus mean salinity values recorded during the study produced a linear relationship for most of the pharmaceuticals (Figure 4). Nine pharmaceuticals—sulfamethoxazole, carbamazepine, diltiazem, hydrochlorothiazide, metoprolol, trimethoprim, valsartan, atenolol, and gemfibrozil—all exhibited a strong linear relationship with high coefficients of determination (r^2), with many exceeding 0.90 (Figure 4), supporting the assertion that rapid removal (e.g., sorption) or degradation processes (e.g., microbial, photolytic, hydrolytic) are

not occurring to a large extent in Narragansett Bay, as that would be reflected by non-linear responses [34]. Rather, the concentrations of pharmaceuticals in Narragansett Bay appear to be affected mainly by dilution. This conservative mixing behavior has been reported for some of the same pharmaceuticals in other urbanized estuaries (e.g., diltiazem, carbamazepine, trimethoprim and sulfamethoxazole) [5,34]. Only caffeine, which was present in every sample, did not exhibit a relationship with salinity or reflect any spatial trends. It is suspected that inputs from non-point sources (e.g., CSOs, leaking septic systems, submarine groundwater), particularly at lower Bay sites including Greenwich and Mount Hope Bays, are a factor in the absence of a gradient. Benotti and Brownawell [35] found a similar lack of correlation between salinity and caffeine concentrations in Jamaica Bay, NY, a sewage-impacted estuary, suspecting either non-point source inputs or microbial degradation.

Temporal trends

There are 6 pharmaceuticals (i.e., gemfibrozil, valsartan, hydrochlorothiazide, carbamazepine, sulfamethoxazole, caffeine) in the dissolved phase that exhibited temporal trends of varying intensity over the term of this study (Figure 2). Four of these pharmaceuticals (gemfibrozil, valsartan, hydrochlorothiazide, carbamazepine) are generally used long-term at consistent dosages for the treatment of chronic conditions (e.g., high cholesterol, high blood pressure), so it can be inferred that other factors were responsible for any apparent trends. For example, gemfibrozil clearly showed both a lower frequency of occurrence and abundance during the June–November sampling periods, standing strongly in contrast to December–March. The trend suggests that gemfibrozil is better preserved in winter months than it is during summer months. Concentration levels of valsartan followed a similar trend. During winter weather periods (e.g., December–March), hydrochlorothiazide also had higher rates of occurrence (88%), contrasting with a much lower presence (34%) during the other months of the year; however, the highest concentrations were recorded at Pawtuxet in August and November, during periods of below average river flow [25]. Caffeine displayed a cluster of elevated concentrations from December–April compared to the other periods, suggesting increased consumption and/or enhanced preservation.

In contrast, carbamazepine displayed a lower rate of occurrence (63%) during the December–March periods when compared to other sampling periods (95%). Concentrations of carbamazepine were relatively consistent over time with the exception of episodic spikes at Pawtuxet Cove and the absence of measurable carbamazepine at several of the lower Bay stations during winter and early spring. This absence during winter and spring months was somewhat unexpected since carbamazepine has been well documented as being resistant to degradation in WWTP systems and natural waters [36,37]. During the December–January sampling periods, sulfamethoxazole had both low abundances and lower presence when compared to the other sampling times. In the summer months (June–August), sulfamethoxazole was elevated, particularly at the Providence River sites. At this time in Pawtuxet Cove there was also a spike in concentration of trimethoprim, which is co-formulated with sulfamethoxazole to treat infections [38].

The other pharmaceuticals did not exhibit discernible temporal trends or were infrequently present, limiting interpretation. Although two of the beta blockers, atenolol and metoprolol, showed episodic spikes in concentration during summer months at Pawtuxet Cove and Fields Point, again due to lower seasonal river flows, a trend was not apparent. Identifiable temporal trends were limited to less than half the pharmaceuticals in the study, with most observations suggesting they were attributable to factors such as season, river flow and temperature [39]. Trends were most prominent at the Providence River stations, which had the highest overall concentrations and percent occurrence. The increases observed during the summer periods, particularly at Pawtuxet Cove, were likely due to reduced river flow from the Pawtuxet (Supplemental Data, Figure S1), resulting in an increased proportion of WWTP effluent [19]. This is also the case for other riverine inputs (i.e., Blackstone) (Supplemental Data, Figure S1) to the upper Providence River, which have experienced reduced river flow particularly during summer months [25], yet relatively consistent effluent discharge volumes. The sites in the mid and lower bay are subject to mixing and rapid dilution, making identification of measurable trends mostly impossible. However, the absence or sporadic presence of measurable pharmaceutical concentrations in these parts of the bay is remarkable and provides temporal information on their overall exposure and fate in the estuary.

Pharmaceutical partition coefficients: K_ds and K_{OC}s

To evaluate partitioning behavior over time and space, coefficients (K_ds) were determined for pharmaceuticals that were measurable in both the dissolved phase and SPM. Four pharmaceuticals—caffeine, carbamazepine, metoprolol and verapamil—were the most frequently measured. Mean values along with their ranges are presented in Supplemental Data, Table S11. Log K_ds for caffeine ranged from 1.07 to 2.72 with a mean value of 1.97, demonstrating a relatively narrow range in variability over time and between all sites. This indicates that differences in sources and local water column conditions did not play an appreciable role in the variability observed (Supplemental Data, Table S11). The log K_d of carbamazepine ranged from 1.28 to 2.87 and had a mean log K_d of 1.95, with values reported from three sites in the Providence River (Fields Point, Pawtuxet Cove and Nyatt Point). As with caffeine values, carbamazepine did not show any discernable trends in K_d between sites and over the study period. Metoprolol K_ds were determined for 6 sites, since it was not detected in the SPM from Newport and North Jamestown. The mean log K_d was 2.24 with a range of 1.63 to 3.27, with no trends evident between sites or sampling periods. Finally, verapamil was present sporadically at 5 sites, with log K_ds ranging from 2.87 to 4.19, and again no spatial trends or temporal trends were apparent. Overall, the range of K_ds observed across sites and time periods provides an estimate of the variability that can be expected for pharmaceuticals under estuarine conditions.

Normalization of K_d values with the fraction of organic carbon (f_{oc}) in the SPM was performed to determine if the f_{oc} reduces and/or explains the variability observed. Calculated log K_{oc}s for caffeine showed a mean value of 3.32 and a range of 2.30 to 4.12, while the corresponding carbamazepine mean log K_{oc} was 3.17, ranging from 2.42 to 4.17 (Supplemental Data, Table S11). The log K_{oc}s for verapamil ranged from 4.42 to 5.46, with a mean of 4.85; metoprolol had a mean of 3.50 and a range of 2.94 to 4.47.

Overall, f_{oc} normalization had no effect on reducing the range of calculated K_{oc}s when compared to those of the original K_ds (Supplemental Data, Table S11). This suggests the affinity of pharmaceuticals for particulates in this study is not dominated by hydrophobic phases like the organic matter associated with the SPM and that other physicochemical variables (e.g., ion exchange, surface complexation, hydrogen bonding [40]) are likely to be playing contributing roles in explaining pharmaceutical sorption behavior in marine systems. The extent of the significance of variables like ion exchange, surface complexation, and hydrogen bonding on pharmaceutical behavior in marine systems is an area of research that needs to be explored.

Ecotoxicity

During the present study, pharmaceuticals resided primarily in the dissolved phase with the highest overall concentrations found at sites within the Providence River. A number of the pharmaceuticals were measured at or near concentrations reported to cause effects in aquatic organisms. Substantial ecotoxicity data exists for carbamazepine, with decreased physical activity reported in amphipods after being exposed to 10 ng/L for 1.5 hours [41]. Nassef et al. [42] observed effects in fish eggs exposed to 12 ng of carbamazepine, while Almeida et al. [43] conducted a 28 day exposure at 30 ng/L and reported biochemical effects after 4 days. Yu et al. [44] reported that sulfamethoxazole had behavioral effects on nematodes at concentrations as low as 0.1 ng/L. Physiological effects from propranolol exposures were measured in mussels at concentrations as low as 0.3 ng/L [45]. Predicted no effects concentrations (PNEC) were calculated for both metoprolol and atenolol at 24 ng/L and 10 ng/L, respectively [46], which are levels below those measured regularly during the present study. The present study demonstrates that PNEC and experimentally derived effects thresholds for a number of pharmaceuticals are being exceeded in the Providence River at times, indicating that biota are being exposed to pharmaceuticals associated with effects under “normal” conditions.

SUMMARY

The physical characteristics, morphology and hydrodynamic processes of Narragansett Bay exerted significant influence on the spatial and temporal distributions and concentrations of dissolved and particulate pharmaceuticals. The concentration and frequency of pharmaceuticals declined with distance from major source inputs in the upper Providence River to the mouth of the Bay, with a strong relationship between most dissolved pharmaceuticals and salinity documenting conservative behavior for many of the compounds. All of the pharmaceuticals resided overwhelmingly in the dissolved phase, resulting in their dilution and eventual transport out of the Bay. Partitioning coefficients (K_d) for 4 pharmaceuticals varied over the course of the study but no spatial or temporal patterns were identified. Normalizing K_ds to the f_{oc} alone had no effect on variability demonstrating the need for more work to better understand the physicochemical variables affecting pharmaceutical partitioning and distributions in marine waters.

Within the Providence River, continuous influx from WWTPs and urban rivers containing effluents resulted in sustained concentrations of pharmaceuticals at elevated levels, creating

a zone of continuous exposure. While this “zone” contains pharmaceuticals identified in the present study, others are present as well, resulting in an unknown level of risk associated with these unregulated chemicals. Increased knowledge of factors controlling spatial distribution, behavior and fate of pharmaceuticals are needed to understand the risk of long-term exposure and possible adverse effects to aquatic life in estuarine systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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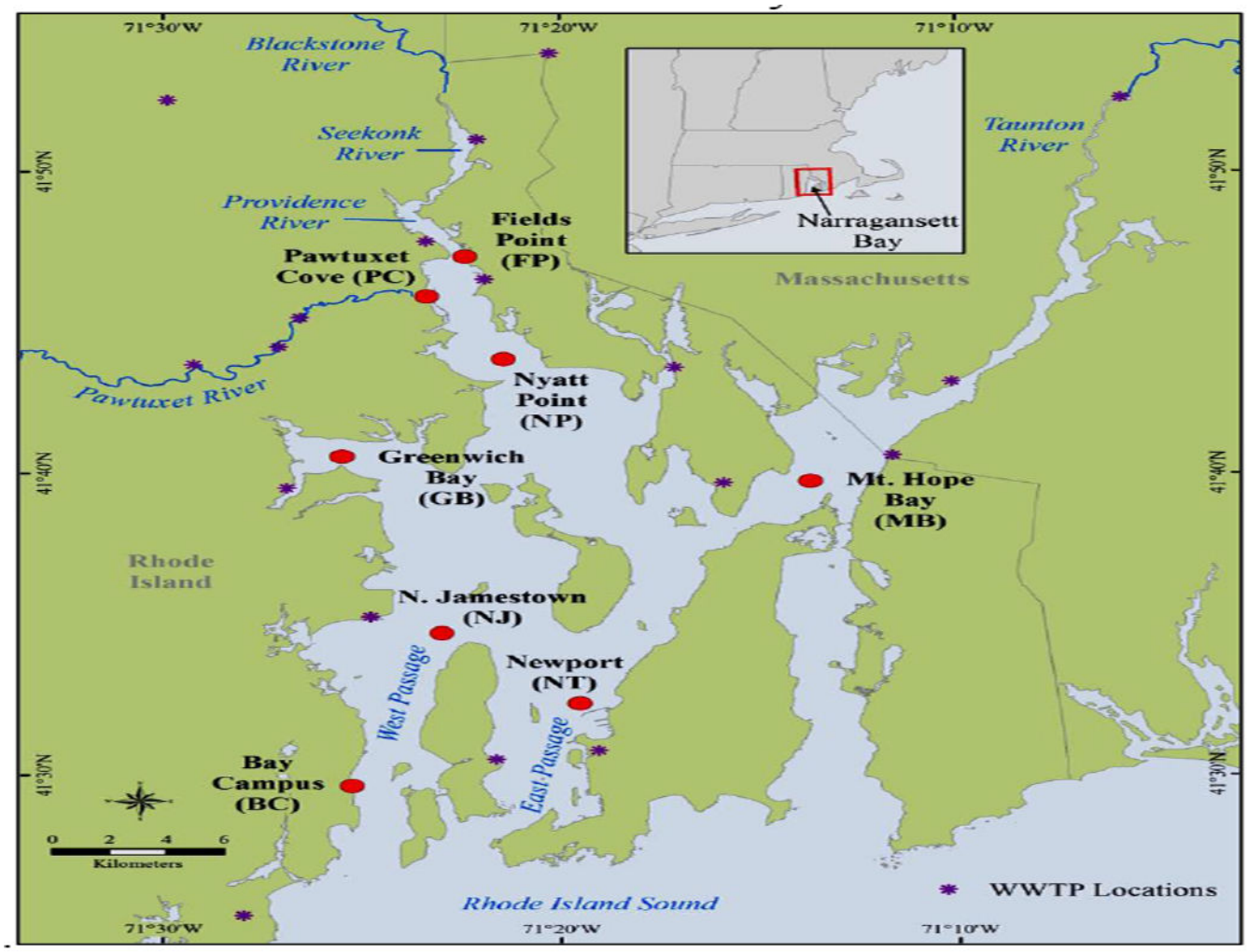

Figure 1.

Map of Narragansett Bay study area with major rivers and sampling sites. Locations of WWTPs in the watershed identified by asterisk.

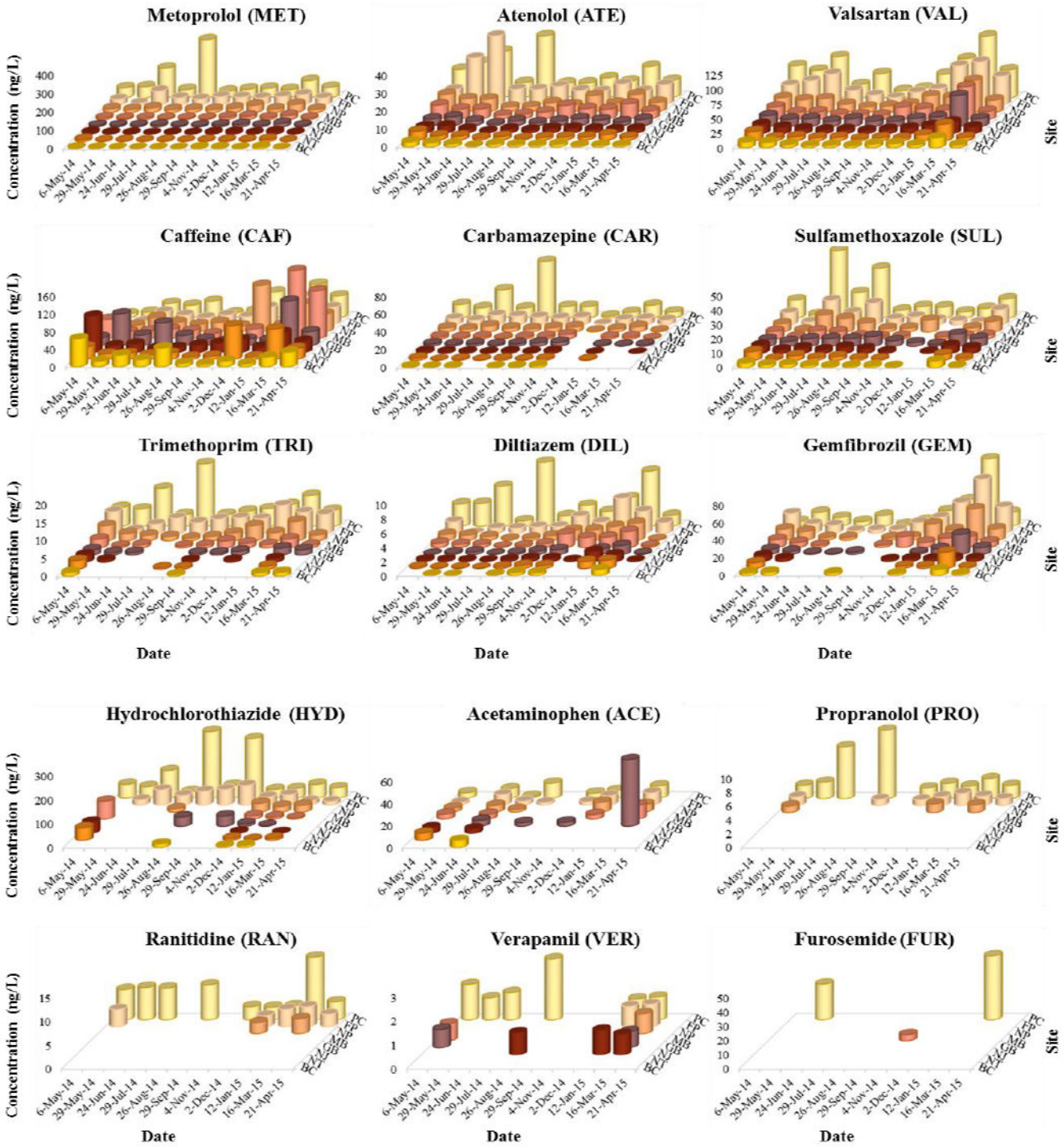

Figure 2.

Concentrations of dissolved pharmaceuticals (ng/L) in the water column arranged by site and sampling period. BC = Bay Campus, NT = Newport, NJ = North Jamestown, GB = Greenwich Bay, MB= Mount Hope Bay, NP = Nyatt Point, FP = Fields Point, PC = Pawtuxet Cove

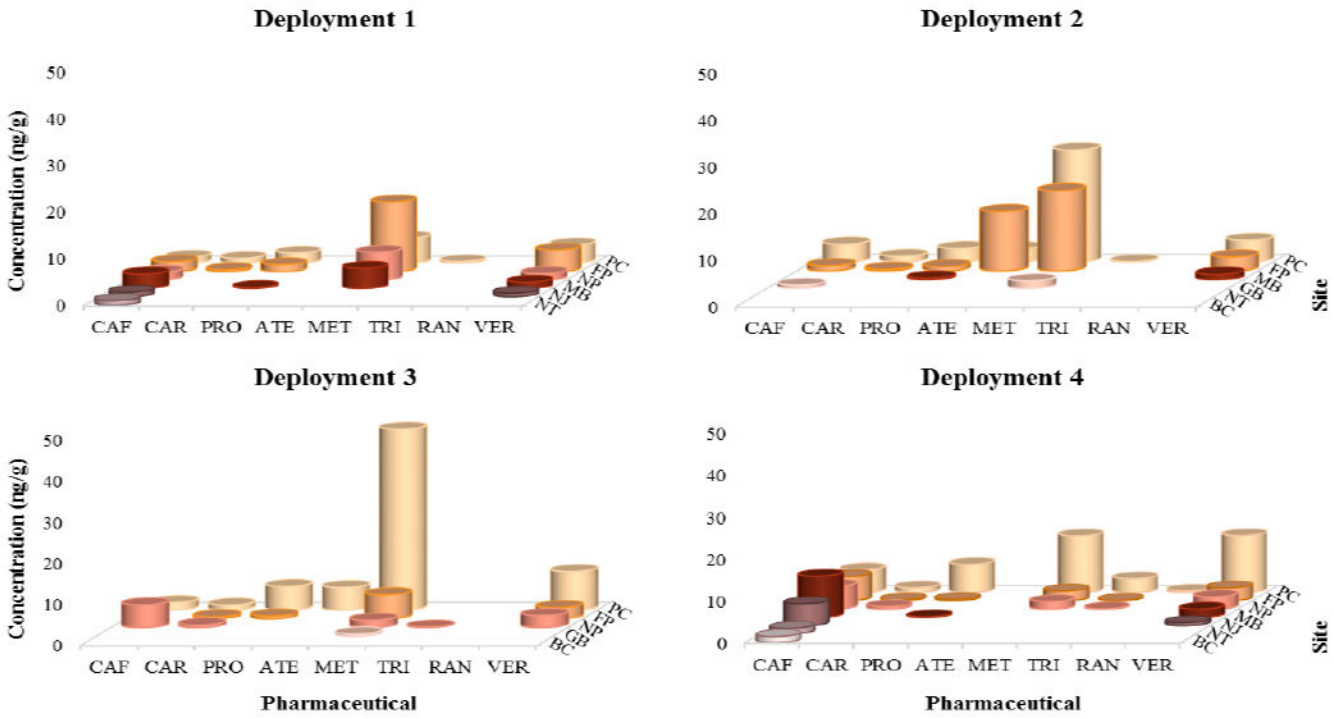

Figure 3.

Pharmaceutical concentrations (ng/g) of particulate matter collected in the sediment traps arranged by site and sampling period. Pharmaceutical concentrations (ng/g) of particulate matter collected in the sediment traps arranged by site and sampling period. CAF = caffeine, CAR = carbamazepine, PRO = propranolol, ATE = atenolol, MET = metoprolol, TRI = trimethoprim, RAN = ranitidine, VER = verapamil; BC = Bay Campus, NT = Newport, NJ = North Jamestown, MB = Mount Hope Bay, NP = Nyatt Point, FP = Fields Point, PC = Pawtuxet Cove.

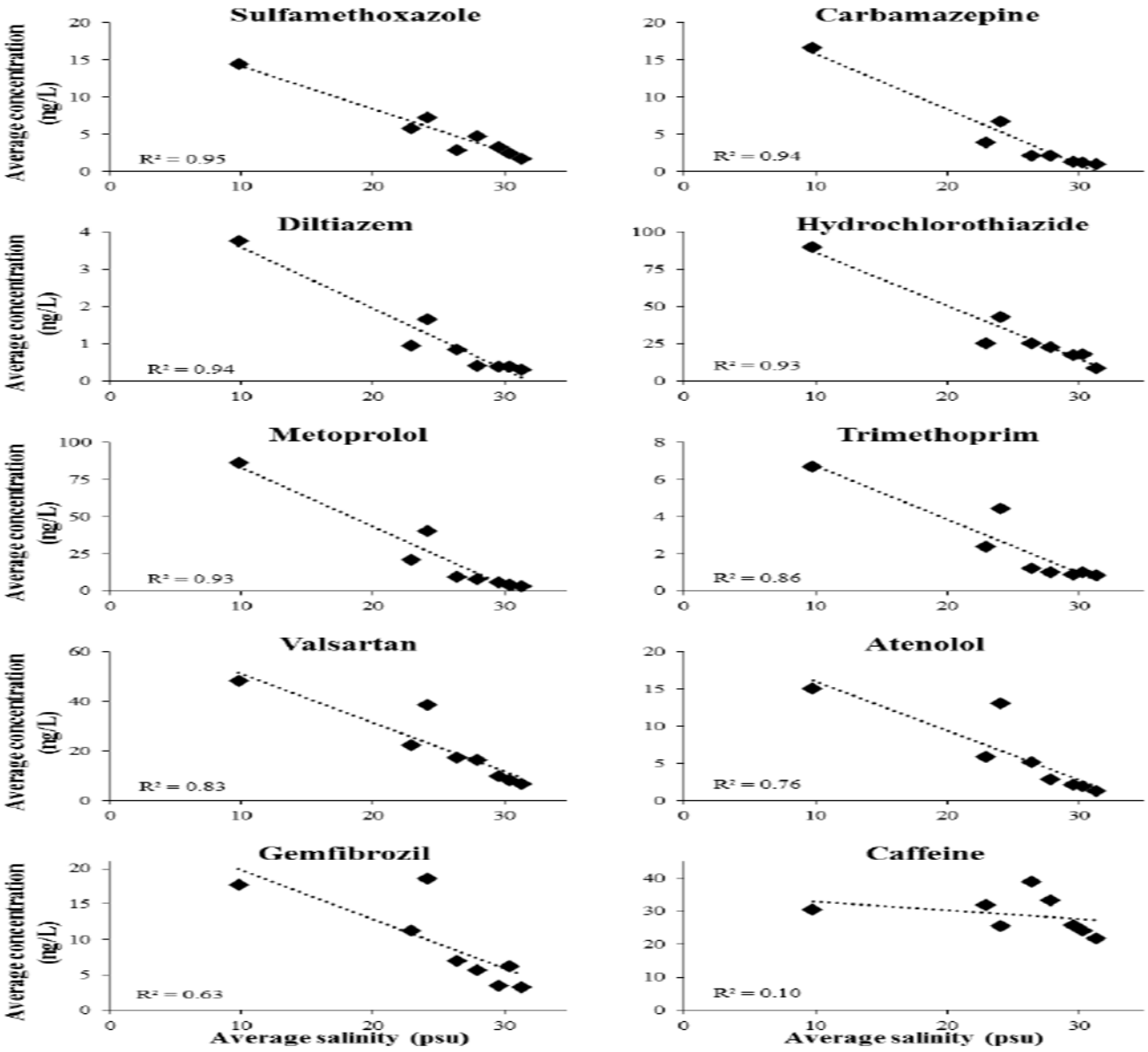

Figure 4.

Salinity-pharmaceutical mixing curves for pharmaceuticals. Compounds with limited data (verapamil, furosemide, ranitidine, propranolol and acetaminophen) are not presented.

Table 1

Classes of pharmaceutical compounds

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Class	Compound	Log K_{OW}
Analgesic	Acetaminophen	0.27
Antibacterials	Sulfamethoxazole	0.48
	Trimethoprim	0.73
Anticonvulsant	Carbamazepine	2.25
Antihypertensives		
Angiotensin Receptor Antagonist	Valsartan	3.65
Beta blockers	Atenolol	−0.03
	Metoprolol	1.69
	Propranolol	2.60
Calcium channel blockers	Diltiazem	2.79
	Verapamil	4.80
Antilipemic	Gemfibrozil	4.77
Antiulcerative	Ranitidine	0.29
Diuretics	Furosemide	2.32
	Hydrochlorothiazide	−0.10
Stimulant	Caffeine	−0.07