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Technical Note

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Improving the Sensitivity of Solid-Phase Microextraction by Reducing the Volume of Off-Line Elution Solvent

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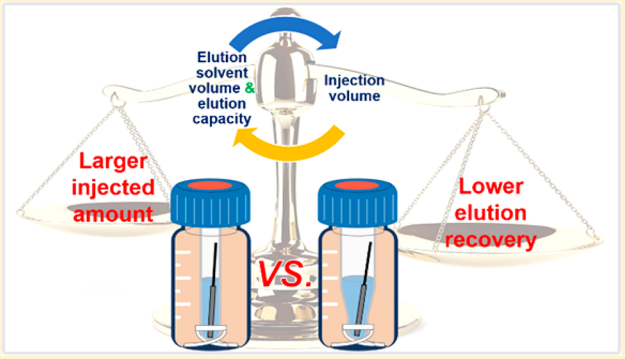
Supporting Information

ABSTRACT: Solid-phase microextraction (SPME) coupled with liquid chromatograph (LC) is widely used to detect polar and ionic organic compounds, including various pharmaceuticals and endogenous bioactive compounds. In this study, a small-sized insert tube for use in the commercial autosampler vial was designed for eluting the extracted analytes from SPME fibers for LC analysis. By using this custom-made insert tube as an alternative to the commercial insert tube, the volume of the elution solvent was reduced by four-fifths. Even though smaller fractions of the analytes were eluted from the fiber coatings, the analyte concentrations in the elution solutions were substantially increased by using the custom-made insert tube. Therefore, larger amounts of the analytes could be injected to LC and higher signal-to-noise ratios could be achieved, even at smaller injection volumes. Since the elution in the custom-made insert tube was nonexhaustive, four strategies were developed to figure out the extracted amounts in the fiber coatings. In combination with the sampling-rate calibration method, these strategies were successfully used to determine the concentrations of fluoxetine in living tilapias. This study provides a simple but effect way for improving the analytical sensitivity when coupling SPME with LC.



Solid-phase microextraction (SPME) is widely used as a sampling and sample preparation technique for environmental analysis,[1] food analysis,[2] biomedical analysis,[3] etc.[4] Being coupled with liquid chromatograph (LC) equipped with different detecttion systems, such as mass spectrometry (MS) and tandem MS, SPME is capable of analyzing polar and ionic organic compounds, including pharmaceuticals and various endogenous compounds,[5−9] which facilitates the applications of SPME in detecting metabolomes[5,6] and exposomes,[7] and studying pharmacodynamics[8] and pharmacokinetics.[9,10]

Eluting the extracted analytes from SPME fibers and subsequently transferring the eluted analytes to LC as thoroughly as possible are important for guaranteeing satisfactory analytical sensitivity. High elution recovery and high transferring efficiency to LC can also be beneficial for cutting down the extraction duration, as well as relieving the steep requirement of improving the extraction efficiencies of SPME fibers.

The eluted analytes in online elution interfaces could be thoroughly pumped into LC for analysis.[11−15] However, the design of online interfaces is rather challenging, which should not only take the elution efficiency into consideration, but also avoid the swelling and exfoliation of the fiber coatings in the interfaces.[12−17] In addition, the volumes and the elution capacities of the elution solvents in the interfaces should be refined to accommodate the inner diameters of the chromatographic columns and the initial gradients of the mobile phases.[16,17] Otherwise, chromatographic peaks could not be as sharp and symmetric as expected, and the signal-to-noise ratios of the chromatographic peaks would be decreased, i.e., the so-called injection effect would be induced.

Off-line elution in specialized vials can be more cost-effective and more efficient than elution in online interfaces, since off-line elution can circumvent the design of complicated interfaces, dozens of fibers can be simultaneously eluted, and the elution procedure can be automated.[18−24] Nevertheless, the elution solution is difficult to be completely transferred to LC for analysis by using any syringes.[21] Besides, the injection volume should also be restricted to prevent the injection effect. To increase the injection volume of the elution solution, solvent of the same composition to the initial gradient of the mobile phase was used for elution.[22] Even a larger volume could be injected, a larger volume of elution solvent was also needed to gain high elution recovery. Therefore, the ratios of

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the analytes injected to LC out of the total extracted amounts might not be substantially increased.[22] Another method adopted pure organic solvent for elution. After that, the organic solvent was evaporated and the residual analytes were redissolved in the solvent of the same composition to the initial gradient of the mobile phase.[21,23] However, the reconstitution step prolonged the sample preparation procedure, and the variation of the redissolution efficiency could probably impart errors to the quantification results.[24] In addition, both of these methods could not overcome the restriction on the injection volumes from the inner diameters of the chromatographic columns.[22,24]

In the present study, a small-sized elution tube was designed to optimize the off-line elution procedure. Larger amounts of the extracted analytes could be injected to LC as the analyte concentrations in the elution solutions were substantially increased. In addition, the corresponding quantification method was also established.

EXPERIMENTAL SECTION

Preparation of SPME Fibers. SPME fibers coated with polystyrene@polydopamine−glutaraldehyde nanofibers were prepared according to ref 25. The diameter of the supporting core of each fiber was 480 μm, and the coating thickness of each fiber was ∼37 μm. The pristine nanofibrous coatings were trimmed to reserve an integrated coating at the end of each fiber, or two segmented coatings on each fiber. The lengths of the integrated coatings were 1.0 cm, the length of each segmented coating was 0.5 cm, and the gap between the two segments was 0.3 cm.

Custom-Made Small-Sized Insert Tube. A small-sized insert tube was designed with a conical opening end, and its inner diameter was much smaller than the commercial insert tube (see Figure 1, as well as Figure S1 in the Supporting Information). The small-sized insert tubes can be used in the commercial autosampler vials being supported by polypropylene feet; the polypropylene feet are the same as those of the commercial insert tubes (see Figure 1, as well as Figure S1). Therefore, the injection of the solutions inside can be automated in any routine LC systems. The inner diameter of the custom-made insert tube is difficult to be further reduced, since the diameter of the LC autosampler syringe needle is ∼1.2 mm in this study. Two hundred pieces of the small-sized insert tubes were made from silica by a private workshop located in Zhejiang Province, China. When the fiber coating was 1.0 cm long, 20 μL of solvent was enough for elution by using the custom-made insert tube, while 100 μL of solvent was needed by using the commercial counterpart. Moreover, when the coating was 0.5 cm long, only 10 μL of solvent was used in the custom-made insert. In the present study, methanol was used for eluting the extracted analytes from the fiber coatings. In some situations, the analytes or their deuterated analogues were spiked in the elution solvent as internal standards for quantifying the extracted analytes in the fiber coatings or calibrating the matrix effects.

Chemicals and Materials, In Vivo Sampling, and Instrumental Analysis. Chemicals and materials are presented in Text S1 in the Supporting Information. In vivo sampling was conducted by following ref 25, as described in Text S2 in the Supporting Information. LC coupled with tandem MS was used for instrumental analysis. The instrumental conditions were referred to ref 25 with little modification; only the analytes and their deuterated analogues were detected in the tandem MS.

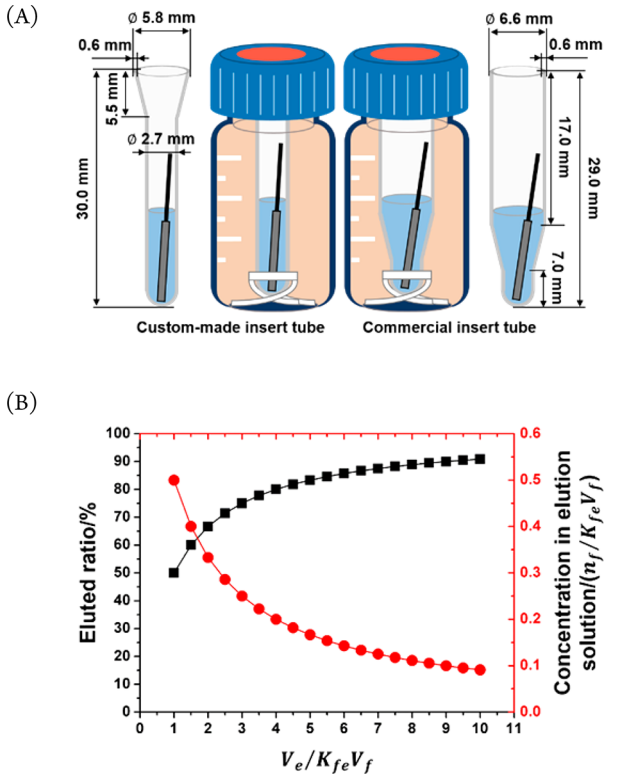

Figure 1. (A) Conceptual diagram of the custom-made insert tube and the commercial insert tube, and their uses in commercial autosampler vials. Plastic feet (at the bottoms of the autosampler vials) were used to support the inset tubes. (B) Eluted ratio and the concentration of the analyte in the elution solution by varying the volume of the elution solvent in eqs 1 and 2.

RESULTS AND DISCUSSION

Theoretical Evaluation of the Effect of Reducing Elution Solvent. Supposing after the partition of the analyte between the fiber coating and the elution solvent reaches equilibrium, the elution is finished. Then, we get

$$\text{Elu.} = \frac{1}{1 + K_{fe}V_f/V_e} \quad (1)$$

$$C_e = \frac{n_f}{V_e + K_{fe}V_f} \quad (2)$$

$$\text{Inj.} = \frac{V_i}{V_e + K_{fe}V_f} \quad (3)$$

where Elu. is the ratio of the analyte eluted from the fiber coating, C_e is the analyte concentration in the elution solution after the elution is over, and Inj. is the ratio of the analyte injected to LC out of the total extracted amount. K_{fe} is the partition coefficient of the analyte between the fiber coating and the elution solvent, n_f is the total extracted amount of the analyte in the fiber coating, V_f represents the volume of the fiber coating, V_e is the volume of the elution solvent, and V_i is the injection volume. The derivation of eqs 1−3 are presented Text S3 in the Supporting Information.

Based on eq 1, it can be concluded that the eluted ratio would be increased by increasing the volume of the elution

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solvent. However, as indicated in eq 2, the analyte concentration in the elution solution would be increased by decreasing the volume of the elution solvent. Then, according to eq 3, larger fraction of the extracted analyte could be injected to the analytical instrument by decreasing the volume of the elution solvent, if the injection volume is not significantly decreased. In addition, according to eqs 1 and 2, when the volume of the elution solvent is reduced, C_e changes much more significantly than Elu. (see Figure 1B). This is the theoretical background for the adoption of the custom-made small-sized insert tube.

Comparison of the Elution Efficiencies between the Custom-Made Insert Tube and the Commercial Insert Tube. First, the elution speed in the custom-made insert tube was compared with that in the commercial insert tube. As shown in Figures S2A and S2B in the Supporting Information, after the elution time exceeding 5 min, the eluted FLX reached the maximum in both the custom-made and commercial insert tubes, which indicated that elution in the custom-made insert tube could be no slower than that in the commercial insert tube. Theoretically, solvent in small-sized tubes is more viscous to be vortexed, which would hinder the elution of the analytes in the small-sized insert tubes. However, smaller inner diameters mean shorter mass-transfer paths in the solvent for the analytes to be eluted from the fiber coatings, which could conversely promote the elution speed in the custom-made insert tubes.

Thereafter, the analyte concentrations in the elution solutions were compared. After extracting FLX and norfluoxetine (NFLX) from phosphate buffer saline (PBS, pH 7.4) solutions, the concentrations of FLX and NFLX recovered in the custom-made insert tubes were determined to be 3.9 and 2.9 times those in the commercial insert tubes (Figure 2A). Similarly, after extracting the analytes from fetal bovine serum, the concentrations of FLX and NFLX recovered in the custom-made insert tubes were determined to be 4.2 and 2.5 times those in the commercial insert tubes (Figure 2B). These results confirmed what was demonstrated in eq 2, that, by reducing the volume of elution solvent, the analyte concentration in the elution solution could be substantially increased.

Moreover, as the concentration ratios between the solutions within the custom-made and the commercial insert tubes were determined, the ratios of FLX and NFLX eluted from the fibers were also determined according to Text S4 in the Supporting Information. In the commercial insert tubes, 93%−95% of the extracted FLX and 75%−82% of the extracted NFLX were eluted from the fiber coatings. Moreover, in the custom-made insert tubes, 73%−79% of the extracted FLX and 38%−48% of the extracted NFLX were eluted from the fiber coatings. These results demonstrated that elution in the custom-made insert tubes was much less exhaustive than that in the commercial insert tubes, as indicated in eq 1. Besides, by comparing FLX and NFLX, it can also be concluded that the analyte concentration would increase more significantly by reducing the volume of elution solvent, when the elution capacity of the solvent is stronger than that of the analyte.

Higher binding affinities of the fiber coatings toward the target analytes could be beneficial for the extraction of the analytes from the sample matrixes. However, the extracted analytes are also difficult to be eluted from the fiber coatings possessing high affinities toward the analytes. On the other hand, both the extraction and the elution of the analytes could benefit from the small mass-transfer resistances within the fiber

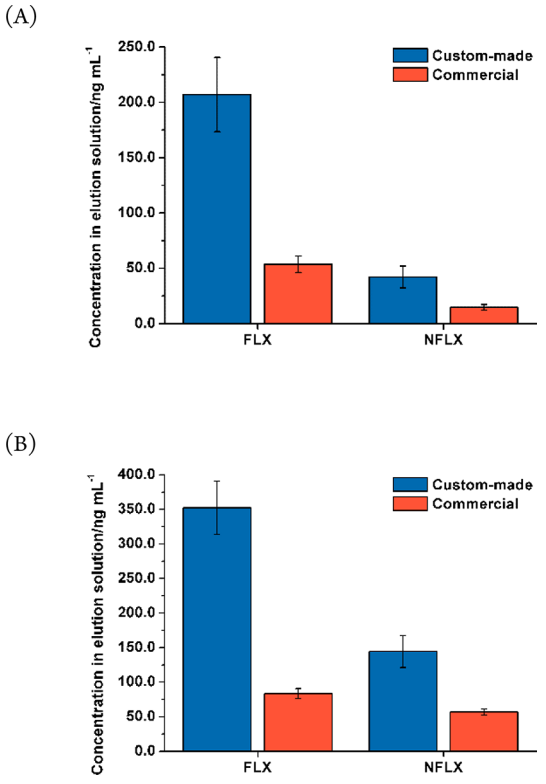

Figure 2. Analyte concentrations in the elution solutions inside the inset tubes. Before elution, fibers extracted analytes from (A) PBS solutions (10 ng mL^{-1}, $n = 6$) or (B) fetal bovine serum (200 ng mL^{-1}, $n = 6$) with the extraction lasting for 60 min. The error bars represent the standard deviations.

coatings. In the present study, the fiber coatings probably possessed higher affinities toward NFLX than FLX, as the eluted ratios of NFLX were smaller than those of FLX. However, the strong noncovalent interactions between the fiber coatings and NFLX might hamper the mass transfer of NFLX within the fiber coatings; the extracted amounts of NFLX in the fiber coatings were smaller than those of FLX (Figure 2A).

Quantifying Extracted Analytes in Fiber Coatings. As demonstrated above, the solvent elution could not be exhaustive by using the custom-made insert tubes. The extracted amounts could not be determined directly by multiplying the analyte concentrations by the solvent volumes in the inset tubes. However, the extracted amounts of analytes in fiber coatings are indispensable for calculating the analyte concentrations in sample matrixes in many widely used calibration methods for SPME.[7,26,27] Therefore, four strategies were developed in this study for quantifying the extracted analytes in the fiber coatings, as shown in Figure 3.

In Strategy I, standard solution was loaded on one segment of each segmented fiber after extraction. After the solvent evaporated, each segmented fiber was severed at the gap between the two segments, and both the segments were eluted in the custom-made insert tubes. Then, the extracted amount could be figured out by comparing the chromatographic peak areas of the elution solutions according to the first equation in Figure 3.

In Strategy II, each segmented fiber was severed at the gap between the two segments after extraction, and one segment was eluted in blank methanol, while the other segment was eluted in solution prespiked with the analytes. The extracted

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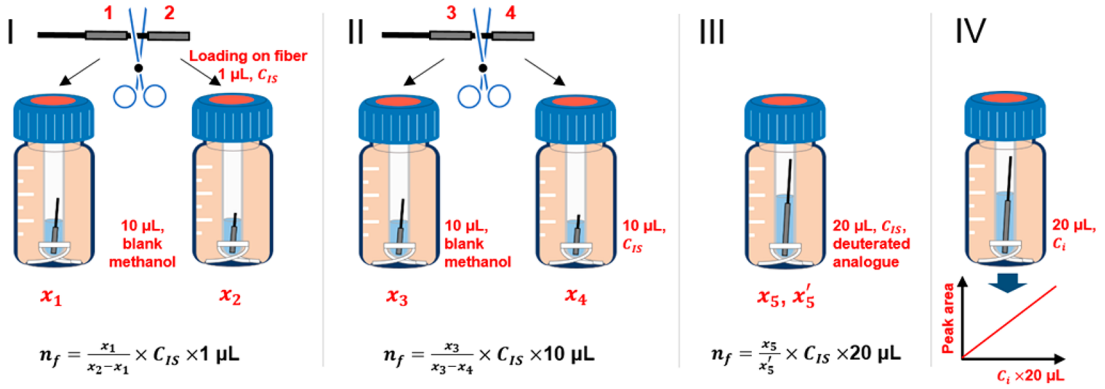

Figure 3. Strategies for quantifying the extracted analytes in fiber coatings. x_1, x_2, x_3, x_4, x_5, and x'_5 all represent chromatographic peak areas.

amount could be determined by comparing the peak areas of the elution solutions, according to the second equation in Figure 3.

In Strategy III, deuterated analogues of the analytes were prespiked in elution solvent for eluting analytes from each integrated fiber after extraction. The extracted amounts could be determined by comparing the peak areas of the analytes and their deuterated analogues according to the third equation in Figure 3.

In Strategy IV, standard curves were plotted for calculating the extracted amounts. First, blank integrated fibers were deployed in a serious of standard solutions prepared in methanol (20 μL in each insert tube), After the analytes reached distribution equilibrium between the fiber coatings and the solvent, the residual analytes in the solution were analyzed. Standard curves were drawn by plotting the peak areas to the initial total amounts of the analytes in the standard solutions (Figure S3 in the Supporting Information). Then, after extraction from sample matrixes, fibers were eluted in 20 μL of methanol, the extracted analytes in the fiber coatings could be determined by replacing the corresponding peak areas in the linear regression equations of the standard curves.

The extracted amounts determined in Strategies I and II should be multiplied by 2 for comparison with Strategies III and IV, since the coating lengths were half of those in the latter two strategies.

Based on the aforementioned four strategies, the amounts of the analytes extracted from PBS solutions and fetal bovine serum were determined and observed to be close to those determined from using the commercial insert tubes (see Figure 4). As discussed above, elution in the commercial insert tubes was also not exhaustive, particularly for NFLX. Therefore, the extraction amounts were determined by multiplying the concentrations of analytes with the volumes of the elution solvent, and then calibrated with the eluted ratios obtained above. Figure 4 demonstrates that the developed strategies could be accurate enough for quantifying the extracted analytes in fiber coatings.

Note that, in Strategies I to III, the amounts of the internal standards should be comparable to that of the extracted analytes to guarantee the accuracy of the obtained extracted amounts. And in Strategy IV, the deuterated analogues were also spiked into the solutions in the inset tubes after elution to calibrate the matrix effects.

In Strategy IV, the partition coefficients and eluted ratios could both be readily determined, as the residual amounts of the analytes could be determined after the fibers were harvested

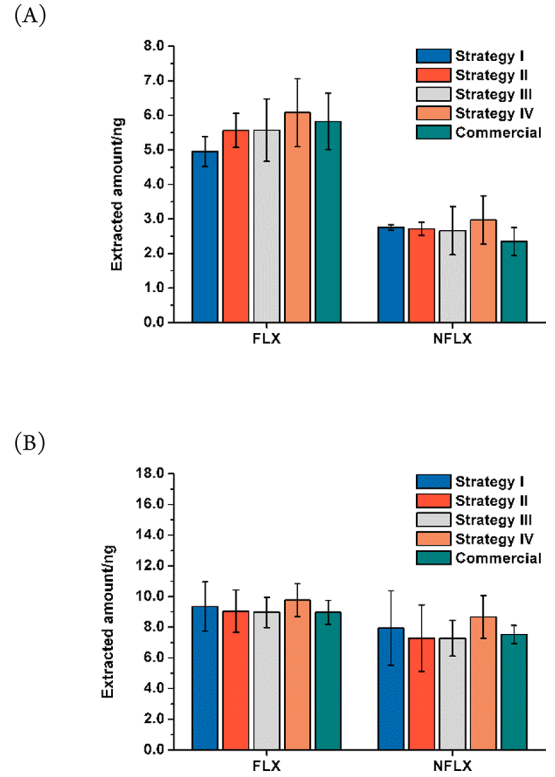

Figure 4. Extracted amounts in fiber coatings from (A) PBS solutions (10 ng mL^{-1}, $n = 6$) and (B) fetal bovine serum (200 ng mL^{-1}, $n = 6$). The error bars represent the standard deviations.

from the standard solutions. Therefore, the eluted ratios were not used to calculate the extracted amounts when using the custom-made insert tubes, which was actually a derived strategy from Strategy IV.

Analyzing FLX in Living Tilapias. Similarly, the aforementioned four strategies were used to determine FLX extracted from the dorsal-axial muscle of living tilapias (*Oreochromis mossambicus*). Thereafter, by using the sampling-rate calibration method,[26] and referring to the sampling rate of FLX previously recorded by our group (123.8 μg min^{-1} ± 13.7 μg min^{-1}),[25] the concentrations of FLX in the dorsal-axial muscle were calculated from the extracted amounts, and were observed to be close to those determined by using the liquid extraction (LE) method (Figure 5A). The *T*-test results also confirmed that the differences among the analyte concentrations determined by different methods were negli-

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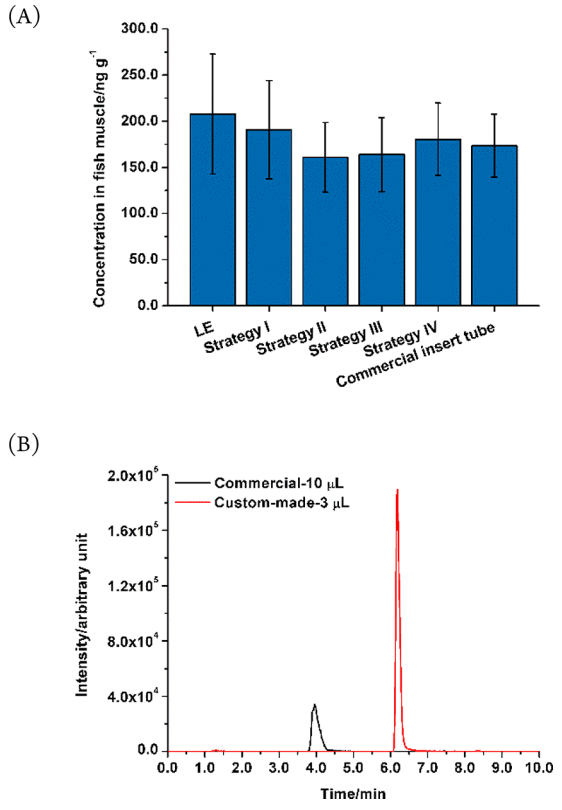

Figure 5. (A) Concentrations of FLX determined in fish muscle (n = 8). In vivo sampling duration was 20 min. The error bars represent the standard deviations. (B) Chromatograms of the elution solutions in the custom-made and the commercial insert tubes. The injection volumes were 3 and 10 μL, respectively.

gible (Text S5 in the Supporting Information). Figure 5A and the T-test results demonstrated that, by coupling the aforementioned four strategies with the existing calibration method, analyte concentrations in living fish could be accurately determined.

It is notable that, by using the custom-made insert tubes to elute the analyte from the fiber coatings, the concentrations of FLX in the elution solutions were also much higher than those obtained by using the commercial insert tubes (see Figure S4 in the Supporting Information). Taking the analysis result of Fish-3 as an example, even at smaller injection volumes (3−10 μL), the injected amount of FLX by using the custom-made insert tube was ∼1.5 times as great as that obtained by using the commercial insert tube, and the signal-to-noise ratio obtained by injecting the elution solution in the custom-made insert tube was 5.6 times as great as that obtained by injecting the elution solution in the commercial insert tube (Figure 5B). It could also be observed in Figure 5B that FLX was eluted from the chromatographic column slower, and the chromatographic peak turned to be sharper and more symmetric by reducing the injection volume, which was because the flow rate of the mobile phase and the organic fraction in the mobile phase were both significantly increased when the injection volume was too large. It might be possible to further improve the quality of the chromatographic peaks by directly using solvent of the same composition to the initial gradient of the mobile phase; however, less amounts of analytes would be eluted from the fiber coatings, compared to that observed using a pure organic solvent.[21−23]

CONCLUSIONS

In the present study, a small-sized insert tube was designed to elute analytes from SPME fiber coatings. Even though the elution recoveries were sacrificed, larger amounts of the analytes could be injected to the analytical instrument, and higher signal-to-noise ratios were obtained. Moreover, four strategies were developed to determine the extracted amounts of the analytes in the fiber coatings because of the nonexhaustive elution in the custom-made insert tubes. Then, in combination with the sampling-rate calibration method, FLX in living tilapias was accurately determined. This study provided the theoretical background for improving the sensitivity of SPME by reducing the volume of elution solvent, and designed a prototype of the small-sized insert tube. Besides, the developed strategies for quantifying the extracted analytes could also be possibly used in other cases when limited solvents were used to elute analytes from SPME extraction phases, for example, when SPME fibers or blades were coupled with ambient MS.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.analchem.7b04777.

Chemicals and materials, in vivo sampling procedure, derivation of eqs 1−3, method for calculating elution ratios, accuracy evaluation, photograph of insert tubes, elution rates, standard curves for calculating extracted analytes, and analyte concentrations in the elution solutions (PDF)

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Notes

The authors declare no competing financial interest.

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