Micelle assisted thin-film solid phase microextraction: a new approach for determination of quaternary ammonium compounds in environmental samples

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ABSTRACT

Determination of quaternary ammonium compounds (QACs) often is considered to be a challenging undertaking owing to secondary interactions of the analytes' permanently charged quaternary ammonium head or hydrophobic tail with the utilized lab-wares.

Here, for the first time, a micelle assisted thin-film solid phase microextraction (TF-SPME) using a zwitterionic detergent 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS) as a matrix modifier is introduced as a novel approach for in-laboratory sample preparation of the challenging compounds.

The proposed micelle assisted thin-film solid phase microextraction (TF-SPME) method offers suppression/enhancement free electrospray ionization of analytes in mass spectrometric detection, minimal interaction of the micelles with the TF-SPME coating, and chromatographic stationary phase and analysis free of secondary interactions. Moreover, it was found that the matrix modifier has multiple functions; when its concentration is found below the critical micelle concentration (CMC), the matrix modifier primarily act as a surface deactivator; above its CMC, it acts as a stabilizer for QACs. Additionally, shorter equilibrium extraction times in the presence of the modifier demonstrated that micelles also assist in the transfer of analytes from the bulk of the sample to the surface of the coating.

The developed micelle assisted TF-SPME protocol using the 96-blade system requires only 30 min of extraction and 15 min of desorption. Together with a conditioning step (15 min), the entire method is 60 min; considering the advantage of using the 96-blade system, if all the blades in the brush are used, the sample preparation time per sample is 0.63 min. Moreover, the recoveries for all analytes with the developed method were found to range within 80.2%- 97.3%; as such, this

method can be considered an open bed solid phase extraction. The proposed method was successfully validated using real samples.

1. INTRODUCTION

Solid phase microextraction (SPME) is a well-established sample preparation method with unique advantages for a variety of applications. SPME boasts flexibility in design, geometry and calibration strategies, and can be used for in-vivo, on-site and in-lab sampling/sample preparation[1]. Amongst its many valuable features, this method shows sensitivity towards changes in the sample; thus, the system under investigation and analytes under interest need to be scrutinized carefully. For instance, analysis of compounds with high affinity to lab-ware such as quaternary ammonium drugs[2], quaternary ammonium detergents[3,4], or compounds with low solubility in aqueous systems such as PAHs[5, 6] may incur inevitable adsorption losses to the lab-wares that are utilized in the sample preparation step. Consequently, erroneous results could be obtained. Although sample preparation in laboratories is frequently affected from such loss of analytes, SPME methods can be easily adapted for on-site sampling, where sampling and sample preparation are combined in a single step and performed directly from the system without any adsorption losses of analytes[7,8]. However, as part of method development, most methods still need to be optimized in a laboratory setting prior to on-site applications.

Solid phase extraction (SPE), frequently considered as the first method of choice in many areas, may also yield similar erroneous results when used in the extraction of challenging analytes such as the ones described above[9]. Quaternary ammonium drugs and surfactants (QACs) constitute one of the well-known groups of compounds that often undergo secondary interactions (nonspecific binding) with lab-wares[3, 10]. The permanently charged quaternary ammonium head interacts with the surface possessing a negative charge, while the hydrophobic long tail (in case of quaternary surfactants) interacts with hydrophobic surfaces. In order to effectively apply SPE and SPME for analysis of QACs, several lab-ware pre-treatment methods with structurally similar compounds or

the corresponding working concentration of the compounds under interest have been reported as a general approach to saturate the secondary interaction surfaces[9,11]. One of the most comprehensive studies up to date for analysis of QACs using SPME has been published recently by Boyaci et al[3]. This study includes evaluation of adsorption losses in a typical sample preparation step, the effects of adsorption losses on the developed method, and the best pre-treatment strategy for elimination/decrease of secondary interactions. The authors reported that among various tested treatment methods, the best strategy was treatment of all utilized materials (sample vials, pipette tips and extraction vessels) with an equivalent concentration of analytes to the working solutions[3]. However, the described treatment method requires additional steps, could potentially introduce human errors, and does not completely eliminate adsorption losses for the most lipophilic compounds (at the lowest tested concentration up to 46% relative error).

Recently, similar problems regarding adsorption losses have been reported for the analysis of quaternary drugs from urine samples[10, 12]. Urine matrix is similar in constituents to environmental aqueous samples. Urine has a leak of matrix components (such as lipids) that can keep the quaternary drugs stable in the sample matrix without loss to the sampling container. To address this issue and show potential solutions, JiJi et al. reviewed the strategies that have been used for elimination of secondary interaction of such compounds with lab-wares[10]. In the mentioned review, 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), Tween 80, Tween 20, bovine serum albumin (BSA), β cyclodextin and sodium dodecylbenzenesulfonate (SDBS) were reported as matrix modifiers to eliminate losses in urinary drug analysis, with special interest for hydrophobic and cationic drugs. Silvester, S.; Zang, F. reported CHAPS as the best candidate for elimination of adsorption-based losses among all abovementioned reagents[12]. CHAPS is a zwitterionic detergent that is widely used as a non-denaturing solvent in purifying membrane

proteins that are insoluble in aqueous solutions due to their hydrophobic nature[13, 14]. It has been shown that this compound does not result in ion suppression or enhancement during liquid chromatography mass spectrometric (LC-MS) analysis. In addition, it has been shown that its use does not cause a decrease in analyte recovery[12]. All these features of CHAPS make it an attractive candidate to test as a matrix modifier for analysis of challenging compounds that possess secondary interactions and for which adsorption losses have been reported for SPME.

The main purpose of this study is to introduce an alternative approach to SPME for laboratory sample preparation of challenging compounds, where complete elimination of the secondary interactions of all tested QACs with the utilized lab-wares is achieved by keeping the final method easily applicable for routine analysis. In this study, for the first time, the applicability of micelle assisted stabilization of quaternary ammonium compounds (QACs) in the presence of CHAPS as a matrix modifier was demonstrated for adsorption loss-prevention in high-throughput SPME analysis from water samples.

2. Experimental

2.1. Chemicals and solutions

The details for chemicals, materials and stock solutions are described in the Supporting Information (Section 1.1 and 1.2).

2.2. Instrumentation

The LC−MS/MS conditions are described in the Supporting Information (Section 1.3).

2.3. Thin film SPME of QACs and evaluation of CHAPS for adsorption losses correction

The experimental details for TF-SPME and evaluation of CHAPS for adsorption losses correction is described in the Supporting Information (Section 1.4 and 1.5).

3. RESULTS AND DISCUSSION

3.1. Preliminary evaluation of the effect of CHAPS on external calibrations of TF-SPME

Preliminary evaluation results on the effect of CHAPS on external SPME calibration plots are shown in Figure 2-S (Supporting Information). For compounds showing adsorption losses (TMTDAC, BAC12, HDTMAC, BAC14, TMODAC and BAC16) a significant improvement in the linearity of external SPME calibration plots was obtained by addition of the matrix modifier. Conversely, for compounds that do not have secondary interactions with lab-wares (TMOAC, DTMAB and DDTAC) the presence of the matrix modifier in the sample opportunely did not possess any adverse effect on the linearity of their external SPME calibrations. Moreover, there was no significant difference in obtained linearity for both tested CHAPS concentrations (1.0 and 3.0 mM).

Results of pre- and post-addition of 1.0 mM CHAPS in samples containing QACs are shown in Figure 3-S (Supporting Information). As can be seen from the figure, for external SPME calibrations, better linearity was obtained with pre-addition of CHAPS into the sampling bottle. However, the linearity of SPME calibrations for post-addition of CHAPS into the collected samples still was substantially improved in comparison to the calibrations obtained in the absence of the matrix modifier.

3.1.1. Evaluation of absolute matrix effect and matrix effect on SPME in presence of CHAPS

Results pertaining to absolute matrix effects (matrix effect on LC-MS/MS) and matrix effects on SPME in the presence of 1.0 mM CHAPS in sample solution for two levels of analyte concentrations are shown in Table 2-S (Supporting Information). Absolute matrix effects at 25.0 ng mL^{-1} and 250.0 ng mL^{-1} of analyte concentrations varied between 90.4% to 100.2% and 86.5% to 91.8%, respectively. On the other hand, substantial variations in matrix effects on SPME were observed for different analytes. For instance, addition of CHAPS resulted in a substantial increase in the extraction amounts of DDTAC, TMTDAC, BAC12, HDTMAC and BAC14 in both tested analyte concentrations. This observation can be attributed to the elimination or decrease of secondary interactions between analytes and the utilized lab-wares; as these interactions were diminished or eliminated, the free portion of analytes available for extraction increased. The abovementioned enhancements were more significant at tested lower analyte concentrations (25.0 ng mL^{-1}). This finding supports the notion that the loss of analytes by secondary interactions to the active sites of the lab-wares is more substantial at low ppb levels. Thus, in the absence of modifiers, external SPME calibrations deviate from linearity as enhancement of response at high concentrations. The extraction of TMOAC and DTMAB (compounds with lower logP values) were not strongly affected by the addition of the matrix modifier, and the observed matrix effect on SPME was within a range of 97.4% - 119.6% for both tested concentrations.

Conversely, the non-polar analytes in the study showed completely different behavior. For instance, a slight decrease on the extracted amount of TMODAC and BAC16 was observed at 25.0 ng mL^{-1} analyte concentration. On the other hand, at 250.0 ng mL^{-1} analyte concentration, an enhancement on the extraction amount of BAC16 was observed. This unexpected observation was evaluated with further experiments, as explained in the following section.

3.1.2. Evaluation of matrix effect at varying CHAPS concentrations

The unexpected behavior of some QACs was further evaluated in another experiment. This experiment was designed to allow evaluation of both absolute matrix effect, and matrix effect on SPME at 25.0 ng mL^{-1} analyte concentration in the presence of 0.1, 1.0, 10.0 and 50.0 mM CHAPS in the sample. In addition, this experiment enabled the determination of the ideal CHAPS concentration needed to completely eliminate adsorption-based losses of analytes. The results of the absolute matrix effect experiment in varying concentrations of CHAPS are shown in Figure 1a. At the studied concentrations of matrix modifier, no absolute matrix effect (signal enhancement or suppression) was observed for the compounds under study.

On the other hand, the effect of the matrix modifier on SPME was more complex in terms of the extraction amount of analytes with varying CHAPS concentration (Figure 1b). For instance, a trend of slight decrease of extracted amounts with increased CHAPS concentration was observed for TMOAC, DTMAB and TMTDAC, both compounds which do not enter into secondary interactions with the lab-wares.

For TMTDAC, BAC12, HDTMAC and BAC14, an increase in the extracted amount of analytes was observed as the matrix modifier concentration in the sampling solution increased, with extraction amount speaking at 10.0 mM, followed by a slight decrease at 50.0 mM of CHAPS. For TMODAC and BAC16, at 0.1 mM of matrix modifier, a decrease in the extracted amount of analytes was observed; this was followed by significant enhancement, reaching maximum extraction at 10.0 mM. By further increasing the CHAPS concentration to 50.0 mM, a slight decrease of extracted amount was observed.

Next, the optimum CHAPS concentration for elimination of secondary interactions was evaluated. This assessment was performed according to the amount of analytes that remained on the extraction plate after a typical SPME. Although all the tested concentrations were promising, it is worth to mention that 10.0 mM of CHAPS is the minimum concentration that needs to be in the sample for effective elimination of secondary interactions (Table 3-S, Supporting Information) for all compounds.

3.2. Extraction time profile

The extraction time profiles of the target compounds in the presence of CHAPS were evaluated and compared to the results obtained in absence of a matrix modifier[3]. Results of this evaluation are shown in Figure 4-S (Supporting Information). In the previous study, where extraction time was optimized in the absence of a matrix modifier, the overall time for extraction had been found to be 45 min[3]. As can be seen from the figure, equilibrium extraction was reached faster in the presence of CHAPS than in the absence of CHAPS. Equilibrium was reached for most compounds (TMOAC, DTMAB, DDTAC, TMTDAC, BAC12 and BAC14) within 15 min, and within 30 min for the other compounds (HDTMAC, TMODAC and BAC16). The observed shorter equilibrium extraction time in the presence of the matrix modifier can be attributed to the facilitated analyte transport produced by analyte-micelle complex present in the static boundary layer. Additionally, the complete elimination of a secondary equilibrium between the analytes distributed in the solution and walls of the 96-well plate can also contribute to the observed faster extraction. All in all, the final TF-SPME protocol only requires 30 min of extraction and 15 min of desorption. Together with a conditioning step (15 min), the entire method only requires 60 min. Considering the advantage of using the 96-blade system, if all the blades in the brush are used, the sample preparation time per sample is 0.63 min.

3.3. Evaluation of various TF-SPME coatings for extraction of QACs from micellar solution

The extraction performances of the frequently used TF-SPME coatings were also evaluated under optimized conditions for micelle assisted extraction. For this evaluation C18, polystyrene divinylbenzene co-polymer with weak anion exchanger (PS-DVB-WAX) and graphene nanoparticles coated TF-SPME were tested and compared to hydrophilic lipophilic balanced (HLB) particles coated TF-SPME for extraction of QACs in absence and presence of micellar solution. Results of this experiment shown in Figure 5-S (Supporting Information) indicate that among the tested coatings, HLB is superior in terms of extraction performance. Contrary, the recoveries for the rest of the coatings were strongly affected from the presence of CHAPS indicating saturation on the extraction phase owing to strong interactions between the extraction phases and matrix modifier.

Moreover, the recoveries for all analytes for HLB coated TF-SPME are close to exhaustive extraction (vary in a range of 80.2%- 97.3%); as such, this method may be considered as an open bed solid phase extraction.

3.4. Theoretical consideration of micellar SPME and micelle assisted stabilization mechanism

The extraction process in the presence of a micellar matrix modifier can be explained in light of the results obtained. As it is shown in the related parts of this article, the first step of inquiry involved proving that the presence of CHAPS in aqueous samples containing QACs can be used to avoid adsorption losses, and that this procedure is more effective when CHAPS is added into the sampling bottle before sample collection. As can be seen in Figure 2, the active surfaces of the lab-wares become saturated by the CHAPS monomers, and once the sample is introduced in the sampling bottle, the analytes are available for extraction. Additionally, it was observed that for

complete elimination of adsorption losses from the 96-well plate, a concentration above the critical micelle concentration (CMC, 3-10 mM[14]) is important, particularly for the most non polar compounds in the study. This also shows that CHAPS is not only saturating the lab-ware surfaces, it is also able to stabilize the analytes in the micelles/sample (Figure 2). Thus, formation of micelles is important to have a method free of adsorption loss. However, there are two main outcomes observed from the formation of micelles that needs to be scrutinized and discussed in details: first, as explained before, the adsorption of most non-polar analytes is eliminated when the concentration of CHAPS is above CMC; second, as the concentration of CHAPS increases, the extraction of analytes decreases. Since it has been proven that the addition of CHAPS eliminates any secondary interactions with lab-wares, the most expected reason for decrease is the association of compounds in the micelles, which may decrease the available free concentration for extraction. Thus, the decrease on the amount of extraction in SPME as the concentration of CHAPS is increased in the sample is strong evidence of a second equilibrium for the distribution of analytes between the bulk and micelles. Although all analytes are homologues and have similar properties, and all of them can incorporate to the structure of micelles, the distribution constant for analytes between the bulk sample and micelles may vary; thus, the amount of analytes extracted at equilibrium can be different for such system.

Additionally, the binding constant (K_b) of each analyte to the micelles can be easily calculated for the compounds that do not show adsorption losses (TMOAC, DTMAB and DDTAC). The simplified equation for equilibrium extraction in SPME (Eqn. 1)[1] defines the dependency of the extracted amount of analyte (n_e) to the distribution coefficient of analyte between the sample and fiber (K_{fs}), volume of extraction phase (V_f) and initial sample concentration (C_s).

$$n_e = K_{fs} V_f C_s \quad (1)$$

The SPME fiber constants in the absence ($(V_f K_{fs})_{\text{Water}}$) and presence of CHAPS ($(V_f K_{fs})_{\text{Micellar matrix}}$) can be used to calculate the K_b which is equal to the ratio of slopes of the regression equations of external SPME calibrations in water (m_W) and in 10.0 mM CHAPS (m_{MM}), respectively (Eqn. 2)[15].

$$K_b = \frac{(V_f K_{fs})_{Water}}{(V_f K_{fs})_{Micellar.matrix}} = \frac{m_W}{m_{MM}} \quad (2)$$

Accordingly, K_b values for TMOAC, DTMAB and DDTAC in 10.0 mM CHAPS were determined as 1.22, 1.17 and 1.14, respectively.

On the other hand, several theoretical models have been proposed to describe the binding analytes in micellar liquid chromatography (MLC)[16-20] can be extended to describe SPME for extraction of analytes from a micellar solution. Among them, the Arunyanart and Cline-Love model is widely used to explain the retention behavior of compounds in MLC separation.

This model assumes association equilibria of an analyte with the aqueous mobile phase, stationary phase and micelles[17]. The hyperbolic dependence of the retention factor (k) to binding constants of analyte for the aqueous solvent/stationary phase (K_{AS}) and aqueous solvent/micelles (K_{AM}) is described by Eqn. 3.

$$k = \frac{\Phi K_{AS}[S]}{1 + K_{AM}[M]} \quad (3)$$

Where Φ is the phase ratio of total volume of mobile phase needed to elute a compound from the column (V_e) to void volume of the column (V_0), $[S]$ is the stationary phase activity and $[M]$ is the micellar concentration.

This theoretical model can be adapted to explain some of the outcomes of this study. The correlation between retention factor (k) in SPE and distribution constant (K_{fs}) in SPME described by Eqn.4 [21] can be used to explain the phenomenon of micellar matrix modification for SPME. In this equation, V_e and V_0 represent the volumes of aqueous sample used for extraction and void volume of the SPE cartridge, respectively.

$$k = K_{fs}\frac{V_e}{V_o} \quad (4)$$

The volume of elution for an analyte from MLC (V_e) can be correlated to the volume of aqueous sample used in SPME (or SPE). Thus, the combination of Eqn. 3 and Eqn. 4 results in a new equation (Eqn. 5), describing the partition of analytes between SPME coating and sample when the extraction is performed from a micellar modified sample matrix.

$$K_{fs} = \frac{K_{AS}[S]}{1 + K_{AM}[M]} \quad (5)$$

Eqn. 5 indicates that K_{fs} is directly proportional to K_{AS}, and in absence of analyte-micellar interaction, it reduces to K_{AS}.

The combination of Eqn. 1 and Eqn. 5 results in Eqn.6 which can be used to determine the amount of analyte extracted by SPME coating in presence of micelles at equilibrium.

$$n_e = \frac{K_{AS}[S]V_f C_s}{1 + K_{AM}[M]} \quad (6)$$

Thus, as it was observed in this study, in the presence of interactions between micelles and analytes, the K_{AS} value may decrease, resulting in lower amounts of extraction.

3.5. Validation of the method

As a part of method validation, intra-day and inter-day precisions were evaluated in three levels of working concentrations (5.0, 25.0 and 250.0 ng mL^{-1}) in water collected from Laurel Creek, located at University of Waterloo. Results of intra and inter-day precisions are shown in Table 4-S (Supporting Information). As can be seen from the table, all results showed good reproducibility, except for inter-day precision of TMOAC at tested lower level (22.9%). LOD, LOQ, regression coefficient of linearity, and accuracy in terms of percent spike recovery from real sample were obtained using external SPME calibration in 10.0 mM CHAPS containing ultrapure water (Table 5-S, Supporting Information). Without any pre-concentration, the LOD and LOQ varied in a range of 0.02 to 0.21 ng mL^{-1} and 0.07 to 0.69 ng mL^{-1}, respectively. If necessary, a pre-concentration step could be incorporated to enhance the sensitivity, however, the obtained detection limits were sufficient for the study. Analytes spike recoveries from real samples were performed at four levels; 0.5 and 5.0 ng mL^{-1} were tested as expected concentrations for the real samples, while higher levels (25.0 and 60.0 ng mL^{-1}) were used to show the applicability of the method over a wide range of analytes concentrations. This supports the applicability of the method as a reliable and fast sample preparation step for such challenging compounds.

4. CONCLUSION

In this study, for the first time, micelle assisted TF-SPME followed by LC-MS/MS was introduced and successfully applied as a novel approach for determination of alkyl and aryl homologues of QACs by use of CHAPS as a matrix modifier in the sample preparation step.

It was found that the best approach for addition of the matrix modifier is to add CHAPS to sampling bottle before collection of the sample. Additionally, it was observed that to achieve complete elimination of adsorption losses, a concentration above the CMC of CHAPS (10.0 mM) is necessary, particularly for the most non-polar compounds in the study. Addition of matrix modifier into the sample (0.1-50.0 mM of CHAPS) did not show sizeable ionization suppression/enhancement for target compounds in mass spectrometric detection. On the other hand, the SPME recoveries were enhanced by addition of CHAPS up to 400% for lipophilic compounds and reached the maximum values in presence of 10.0 mM CHAPS in the sample. The validity of the method was demonstrated by spike recovery from water collected from Laurel Creek, located at the University of Waterloo. The percent spike recoveries were determined to vary in a range of 82.6 - 110% over a wide range of tested analyte concentrations.

Results indicate that combination of the selected coating (HLB) and micelle assisted stabilization of the analytes in the sample constitute a new approach for safe in vitro sample preparation for detection of sticky compounds. Currently we are moving the described strategy for more challenging matrices. Interesting extension of this work is extraction of solid sample using water-detergent mixtures. Our initial data are encouraging and will be reported upon completion of the studies. The proper choice of the detergent/extraction phase pair can likely facilitate effective extraction of other difficult analytes. In particular this approach is very interesting when biodegradable detergents are used resulting in green extraction technology.

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SUPPORTING INFORMATION AVAILABLE

Additional information is available as noted in text. This information is available free of charge via the Internet at http://pubs.acs.org/.

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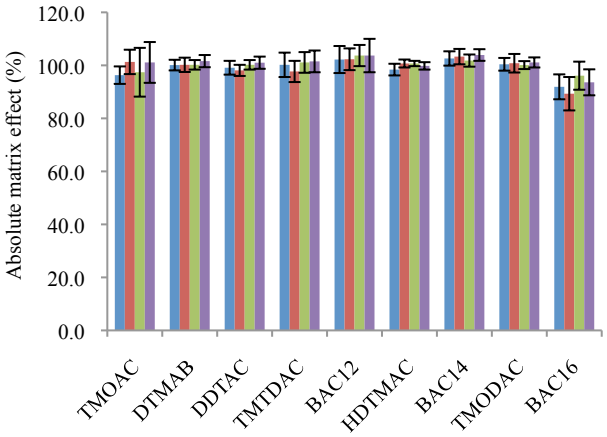
FIGURE CAPTIONS

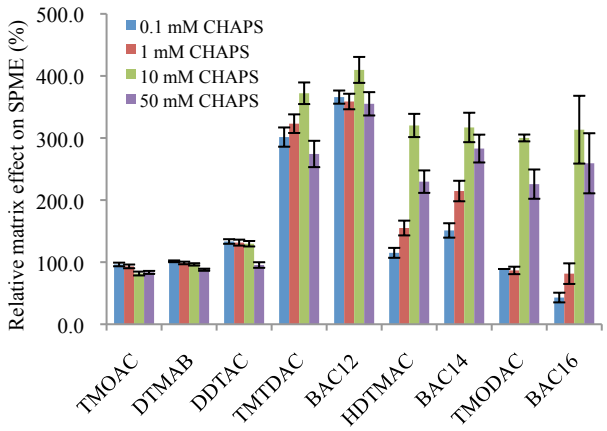
Figure 1. Matrix effects in various concentrations of CHAPS (analyte concentration: 25.0 ng mL^{-1}) a) absolute matrix effect and b) relative matrix effect on SPME

Figure 2. Dynamic process in a typical micelle assisted TF-SPME

FIGURES


120.0
100.0
80.0
60.0
40.0
20.0
0.0
Absolute matrix effect (%)
TMOAC
DTMAB
DDTAC
TMTDAC
BAC12
HDTMAC
BAC14
TMODAC
BAC16

(a)


500.0
400.0
300.0
200.0
100.0
0.0
Relative matrix effect on SPME (%)
0.1 mM CHAPS
1 mM CHAPS
10 mM CHAPS
50 mM CHAPS
TMOAC
DTMAB
DDTAC
TMTDAC
BAC12
HDTMAC
BAC14
TMODAC
BAC16

(b)

Figure 1. Matrix effects in various concentrations of CHAPS (analyte concentration: 25.0 ng mL^{-1}) a) absolute matrix effect and b) relative matrix effect on SPME

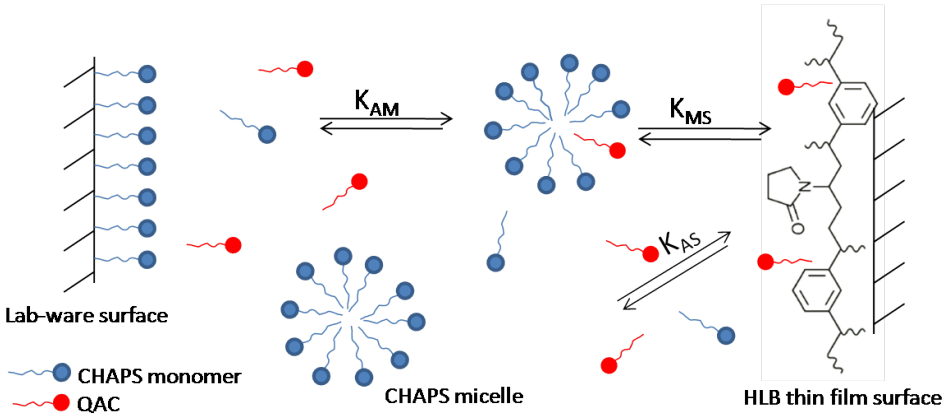
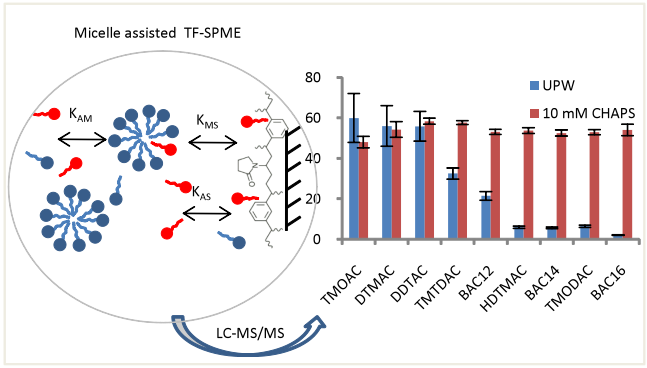


Figure 2. Dynamic process in a typical micelle assisted TF-SPME

“For TOC only”


Micelle assisted TF-SPME
K_{AM}
K_{MS}
K_{AS}
LC-MS/MS
80
60
40
20
0
UPW
10 mM CHAPS
TMOAC
DTMAC
DDTAC
TMTDAC
BAC12
HDTMAC
BAC14
TMODAC
BAC16