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Technical Note

Fabric-Phase Sorptive Membrane Array As a Noninvasive *In Vivo* Sampling Device For Human Exposure To Different Compounds

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Cite This: *Anal. Chem.* 2021, 93, 1957−1961

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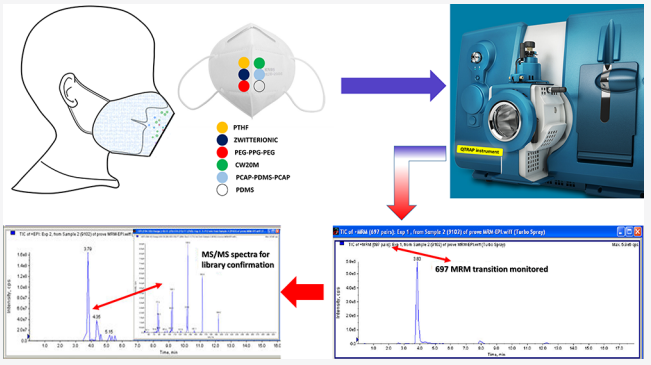
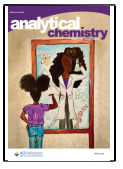
ABSTRACT: This study introduces an innovative device for the noninvasive sampling and chromatographic analysis of different compounds present in exhaled breath aerosol (EBA). The new sampling device, especially in light of the recent COVID-19 pandemic that forced many countries to impose mandatory facemasks, allows an easy monitoring of the subject's exposure to different compounds they may come in contact with, actively or passively. The project combines the advantages of a fabric-phase sorptive membrane (FPSM) as an *in vivo* sampling device with a validated LC-MS/MS screening procedure able to monitor more than 739 chemicals with an overall analysis time of 18 min. The project involves the noninvasive *in vivo* sampling of the EBA using an FPSM array inserted inside an FFP2 mask. The study involved 15 healthy volunteers, and no restrictions were imposed during or prior to the sampling process regarding the consumption of drinks, food, or drugs. The FPSM array-LC-MS/MS approach allowed us to effectively exploit the advantages of the two complementary procedures (the convenient sampling by an FPSM array and the rapid analysis by LC-MS/MS), obtaining a powerful and green tool to carry out rapid screening analyses for human exposure to different compounds. The flexible fabric substrate, the sponge-like porous architecture of the high-efficiency sol−gel sorbent coating, the availability of a large cache of sorbent coatings, including polar, nonpolar, mixed mode, and zwitterionic phases, the easy installation into the facemask, and the possibility of sampling without interrupting regular activities provide FPSMs unparalleled advantages over other sampling techniques, and their applications are expected to expand to many other clinical or toxicological studies.



In recent years, an increasing amount of attention was paid to the development of new technologies and innovative devices able to monitor, through noninvasive sampling, the levels of human exposure to different compounds present in the environment. In the past, different sampling systems were used to monitor the surrounding air, but the recent global pandemic situation and the mandate to wear protective facemasks opens up a new opportunity to evaluate a novel exposure monitoring system that minimizes the shortcomings of conventional environmental sampling and allows the sampling of exhaled breath from the subject while wearing the facemask. Filter masks (such as N95 (USA), KN95 (China), and similar) are now mandatory in many countries as they protect the subjects from unintended exposure to viruses.[1,2] When the facemask is on, exhaled breath aerosol (EBA) containing water molecules, volatile and nonvolatile compounds, microdrops, and particles of biological origin are effectively blocked inside the mask and create a sort of "microenvironment" inside the facemask, which is extremely interesting in terms of an analytical clinical point of view as it is enriched with numerous metabolites and biomarker compounds that are easily exploitable for diagnostic purposes.[3−5] These compounds actually represent chemicals to which the subject was exposed (at an environmental level or following intake through diet or lifestyle habits) as well as biomarker(s) pertaining to any specific disease condition. In the analytical clinical field, the great developments in the fields of mass spectrometry (MS) and tandem mass spectrometry (MS/MS) in terms of sensitivity and selectivity as well as at the software level (in terms of signal acquisition procedures and the switching speed between the positive and negative ionization modes) have certainly made them the diagnostic tools of

Received: November 4, 2020
Accepted: January 8, 2021
Published: January 20, 2021



https://dx.doi.org/10.1021/acs.analchem.0c04663
Anal. Chem. 2021, 93, 1957−1961

choice among all the currently available detection and identification techniques.[6−8]

Fabric-phase sorptive extraction (FPSE), a new-generation sample preparation technique that was developed to integrate conventional solid-phase extraction (SPE) and solid-phase microextraction (SPME) and simplify the overall sample preparation workflow, has already demonstrated its potential as a green sampling and sample preparation procedure for conventional (plasma and urine)[9−11] and unconventional (whole blood and saliva)[12−14] complex matrices. If the recent developments of LC-MS or LC-MS/MS are effectively coupled with the great potential already demonstrated by fabric-phase sorptive membranes (FPSMs), there is no doubt that a new direction of EBA analysis would open up, leading to the discovery of novel disease biomarkers based on exhaled breath, a new exposure monitoring regimen, and routine clinical well-being monitoring protocols via EBA, to name a few. The FPSE combines the advantages of the exhaustive extraction typical of SPE procedures with the advantages of the equilibrium extraction typical of SPME, overcoming the drawbacks of both techniques (device saturation, possible occlusion, and surface area usable for the extraction procedure). Furthermore, the open configuration allows the interchange with the surrounding environment, the transfer kinetics, and the efficiency of the membrane−analyte interaction to be maximized. Using an FPSM is a much safer approach than using an SPME fiber due to its fragility and low surface area since the FPSM can perform much better than its counterpart due to its flexibility, high surface area, open-bed SPE characteristics.[8] Furthermore, the FPSM has remarkable mechanical, thermal, and chemical stabilities since the adsorbent phase is covalently bonded to the flexible fabric support. The special planar geometry of FPSMs provides an open-bed configuration able to facilitate and accelerate the selective sorption and desorption of target compounds. A new FPSM coated with a mixed-mode zwitterionic sorbent has also been recently developed and is herein applied for the first time, where it is capable of simultaneously adsorbing acidic, basic, and neutral compounds.

In this technical note, an innovative device for standardized, noninvasive, and *in vivo* EBA sampling and screening is developed for the first time based on an array of FPSMs with different surface chemistries that are able to provide sensitive screening results regarding the exposure of the subject to more than 739 different compounds in an LC-MS/MS both at an environmental level and as a result of intake through diet or lifestyle habits (i.e., smoker or not, intake of coffee or other) with analysis time of 18 min using deuterated internal standards. This device and the resulting protocol effectively exploit the qualities and advantages of the FPSE technique with the large analytical flexibility of tandem mass spectrometry and provide a universal, safe, economical, convenient, effective, and simple screening method for EBA on a large scale, which can also be deployed in the monitoring and evaluation of occupational health risk assessment (OHRA) and occupational health practice (OHP).

EXPERIMENTAL SECTION

Materials and Instrumentation. Fabric-phase sorptive membranes were synthesized in the Department of Chemistry and Biochemistry at Florida International University using standardized and published protocols.[15,16] The facemasks, all FFP2 (same batch, KN95-approved according to EN149:2001 + A1:2009 and compliant with GB2626−2006), were purchased from the local pharmacy (see Figure S1). The kit containing the deuterated chemical standards and mobile phases for LC-MS/MS analyses was purchased from the Eureka srl Lab Division (code SC9000). The complete list of analytes (also with collision energies and MRM transitions) is reported in Table S1. The LC-MS/MS instrumentation used herein was an ABSciex API 4500 QTrap coupled with a Shimadzu Nexera X2 LC system (a SIL-30AC autosampler, a LC-30AD pump, and a CTO-20AC column oven). All measurements were carried out in the Pharmatoxicology Laboratory of Santo Spirito Hospital, which was accredited by ACCREDIA (laboratory no. 2274 ASLPE, accreditation no. 1822L) according to ISO/IEC 17025 for the analysis procedures. All instrument settings (for LC and MS) are detailed in the Tables S2 and S3, and Figures S2 and S3.

FPSM Array: Facemask Device Preparation and EBA Sampling. To maximize the retention of the target compounds present in EBA possessing a broad range of polarities and other physicochemical properties, an FPSM array was built with membranes possessing widely varied sorbent chemistries as follows: nonpolar sol−gel PDMS; medium-polar sol−gel PTHF, sol−gel PEG−PPG-PEG, and sol−gel PCAP−PDMS-PCAP; and polar sol−gel CW20 M and mixed-mode zwitterionic sorbent. All the membranes used in the array for the noninvasive *in vivo* sampling of EBA were previously cut with a puncher (diameter of 1 cm corresponding to a surface area equal to 0.785 cm^2) to obtain membranes with reproducible dimensions (standardization of the sampling device, as reported in Figures S4 and S5). The individual FPSMs that composed the array were then activated and cleaned (Figure S6) per the published protocols.[8−13] Subsequently, the dried membranes were inserted inside the facemask, in the same position for all the masks, and immobilized by stapling (as indicated in Figure S7). The positions of the arrays inside the mask were arranged is such a way that the lips never come into contact with them as they were placed about 2−3 cm away. Furthermore, the dimensions of the array are such that the filtering capacity of the mask, the resistance to breathing of the subject, and above all the degree of protection offered by the device remained unchanged, as reported in Figure 1.

For the blank analysis, the facemasks containing the six membranes were left in the workplace in a closed studio (environmental blank) and in a sterile and isolated box (device blank). With regard to the sampling procedure, 15 healthy

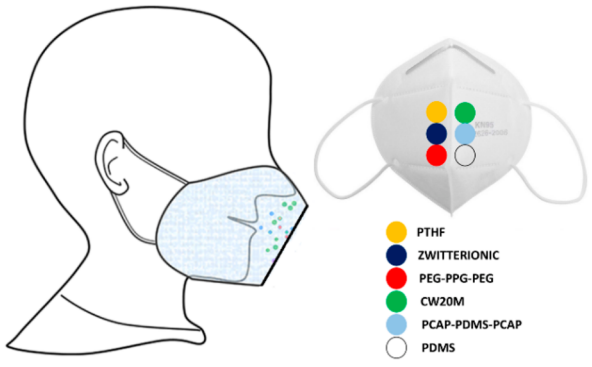


Figure 1. Facemask and FPSM array (with the different membrane positions).

https://dx.doi.org/10.1021/acs.analchem.0c04663
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volunteers (5 males, 10 females) wore the mask over a full working day (approximately 8 h), respecting the current national regulations in force on social distancing and the inherent rules for the use of facemasks in Italy. All volunteers signed an informed consent form for EBA sampling and were not imposed any restrictions on the consumption of drinks, food, cigarettes, or drugs, nor were any specific inclusion or exclusion criteria considered. More detailed information pertaining to the volunteers is reported in Table S4. At the end of the sampling period, the FPSM arrays were separated from the masks and subjected to the back-extraction protocol described in the following paragraph.

FPSM Array Back-Extraction and LC-MS/MS Analysis. After removal from the FFP2 mask, the membranes were subjected (all membranes together) to a back-extraction procedure during where, through the use of MeOH containing the deuterated chemical standards, the analytes adsorbed on the membranes during EBA sampling were recovered. The process involves the following steps: (*i*) removal of the membranes, (*ii*) immersion of the membranes in the "Reagent A″ of the kit (methanol containing the deuterated chemical standards), (*iii*) centrifugation at 12000*g* for 10 min, (*iv*) 1:1 (*v*:*v*) dilution with "Reagent E″ (water with a $ZnSO_4$ stabilizing solution), (*v*) vortex, and (*vi*) injection of 30 μL of sample into the LC-MS/MS system. The LC-MS/MS method was optimized for the screening analysis results in a rapid elution gradient and a change in the flow rate during the chromatographic run. The initial conditions are 90% (A) and 10% (B). The chromatographic column is a Restek Allure PFPP (5 μm, 60 Å, 50 × 2.1 mm), which was thermostated at 40 °C (±1 °C). Detailed information about the gradient is reported in Table S2. With regard to the mass spectrometer, the response potential derived from the QTrap configuration and the management software was exploited. In fact, the instrument works in the multiple reaction monitoring (MRM) mode on 697 specific transitions for the list of compounds subject to screening. When the MRM signal intensity exceeds the set threshold value, the "Enhanced Product Ion" (or EPI) mode is activated in which the complete fragmentation of the molecular ion is obtained to record a MS/MS spectrum that can then be compared with the mass spectra present in the library to confirm the presence of the compound and its correct identification. The threshold value was set on the basis of the signal-to-noise ratio (S/N) obtained by injecting a mixture of chemical standards at the cutoff concentration level required by law (~300 ng/mL for illicit drugs in particular). Furthermore, this value, equal to 8000 count per second (cps), was also chosen to avoid the molecular ions all fragmenting (too low) or never fragmenting (too high).

RESULTS AND DISCUSSION

FPSM Array-LC-MS/MS Method. The acquisition procedure applied to MS/MS allowed us to increase the qualitative analytical information[17] and obtain a series of fundamental advantages: (*i*) increased selectivity as at least two MRM transitions were considered, increasing the degree of confidence in the identification of the compound; (*ii*) increased sensitivity because the fragments were accumulated in the last sector of the mass spectrometer in the EPI fragmentation process, achieving a higher signal-to-noise ratio; (*iii*) increased analytical information as the various EPI spectra were automatically acquired by exploiting the rationality provided by Information Dependent Acquisition (IDA), the Dynamic Background Subtraction (DBS), and the Dynamic Fill Time (DFT); and (*iv*) an immediate comparison of the acquired MS/MS spectra with the database to correctly identify the compound. By applying this procedure, it was therefore possible to monitor hundreds of chemicals to which a subject can be exposed. Furthermore, thanks to the increased sensitivity given by the FPSM array-LC-MS/MS configuration, it was possible to monitor the presence and absence of the analytes in the EBA. The following paragraph shows the results derived from the analysis of real samples.

EBA Screening Analysis. Following the application of the LC-MS/MS configuration of the particular signal acquisition procedure and of the innovative FPSM array (also with the use of a new type of mixed-mode zwitterionic membrane capable of adsorbing neutral, acidic, and basic compounds), it was possible to monitor the levels of exposure in 15 healthy subjects directly through the EBA analysis. Figure 2 shows an example of the "positivity" of the FPSM array to nicotine, caffeine, and ketoprofen and how the total ion current (TIC) MRM and fragmentation spectrum is reported by the system for identification through the EPI procedure.

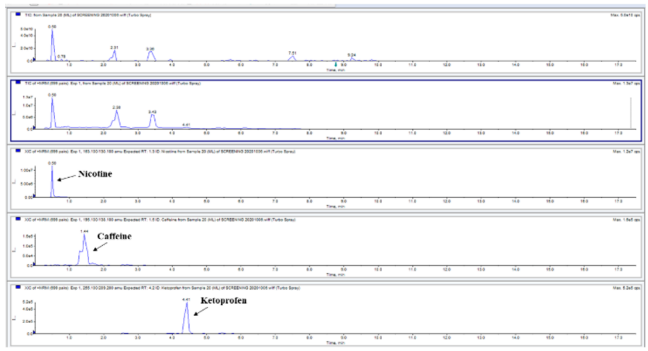

Figure 2. TIC MRM and MS/MS spectra for a sample positive to nicotine, caffeine, and ketoprofen.

The results obtained from this study are reported in Table 1, where the positivity values for the compounds indicate the presence in each subject. The chromatographic profiles for each subject are reported in Figure S8.

Table 1. Chemicals Observed in the 15 Healthy Volunteers after the FPSM Array-LC-MS/MS Procedure

sample ID	nicotine	caffeine	ketoprofen
1	√	√	√
2		√	
3		√	
4	√	√	
5		√	
6		√	
7	√		
8			
9		√	
10		√	
11		√	
12	√	√	
13	√	√	
14		√	
15		√	

https://dx.doi.org/10.1021/acs.analchem.0c04663
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However, the nicotine-related signal was also found in nonsmokers subjects, although at very low concentrations compared to smokers. This could be due to involuntary exposure to environmental tobacco smoke (ETS) or "passive smoking" that may occur at homes, at workplaces, and in public areas. ETS has a different chemical-physical composition than traditional smoke (MS), i.e., the smoke that the smoker inhales. ETS consists of a smaller quantity of smoke that escapes during aspiration or diffuses through the cigarette paper into the environment. Once these substances are released, they can aggregate with pollutants already present in the environment and therefore change their character. ETS is one of the most important air contaminants, and several studies have been conducted on the damage caused by exposure to ETS compared to active smoking. In fact, ETS has been declared a carcinogen by the International Agency for Research on Cancer (IARC). Other drugs not included in the screening that volunteers took (birth control pill, antihistaminic, etc.) were not detected or not present in the compounds list. In blank samples, the nicotine peak was not found, possibly due the fact that the facemasks were left indoors in a place where smoking is prohibited (workplace) and the air was not contaminated.

Furthermore, it should be emphasized that similar approaches are not reported in the literature, both in terms of *in vivo* and noninvasive sampling and in terms of the high number of compounds that can be monitored. Until now, in fact, the works involved the direct analysis of the air or aerosol dispersed in the atmosphere[18,19] or, as recently reviewed by Sanchez-Prado,[20] through the invasive sampling of a biological matrix (blood) to monitor the metabolites of active ingredients present in the environment, followed by a "classic" extraction (microwave) and analysis procedures.

Green Analytical Procedure Index (GAPI). Recently, renewed attention has been paid to the demand that new devices and procedures should be as "green" as possible. Regarding this, Płotka-Wasylka reported an interesting article about the GAPI index (green analytical procedure index).[21] By following the parameters indicated in this approach and critically evaluating the individual elements of the entire procedure (solvents, energy consumption of the instrumentation, quantity of discharges, etc.), it was possible to develop a pictogram that visually gives an idea of how green the proposed device or procedure is. It should be emphasized that the procedure and the innovative configuration shown here demonstrate a fairly good "green" profile based on the GAPI index. Figure 3 shows the pictogram derived from the application of these parameters. STable S5 and Figure S9 report (with an explanation of the pictogram) the specifications relating to the method and the corresponding color.

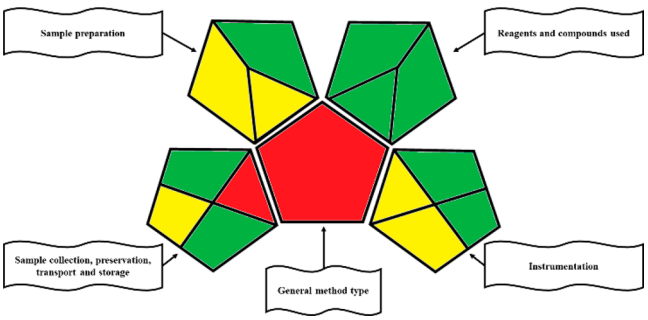

Figure 3. GAPI pictogram for the reported innovative device and procedure.

CONCLUSIONS

In this technical note, an innovative device for standardized, noninvasive, and *in vivo* EBA sampling and screening is presented for the first time. This device, based on an array of fabric-phase sorptive membranes with different surface chemistries, is able to monitor human exposure to more than 739 different compounds using an LC-MS/MS, with analysis time of 18 min, both at an environmental level and as a result of intake through diet or lifestyle habits. This instrument configuration leads to a synergistic effect of the qualities and advantages of the FPSM array (herein presented for the first time) technique with the extreme analytical flexibility of LC-MS/MS, obtaining an exceptionally beneficial tool to monitor and evaluate the occupational health risk assessment (OHRA) and occupational health practice (OHP).

In addition, the procedure proposed here resorts to the use of deuterated internal standards that allow the complete control of the system (retention times and fragmentation conditions). This device represents, to date, the only one able to carry out a first-level analysis (screening) on such a wide range of molecules through noninvasive *in vivo* sampling in very short times, speeding up of the process that leads to a targeted second-level analysis (quantitative). Another important element to underline is the green profile of the entire procedure based on the GAPI pictogram, which leads us to consider it as a highly recommended application for chemical-clinical laboratories that do a lot of routine analyses as it reduces or limits the environmental impact derived from these activities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.analchem.0c04663.

Photographs of instruments and equiptment, analyte list with collision energies and MRM transitions, gradient elution profile and instrument configuration information, mass spectrometer procedures, detailed information on the 15 healthy volunteers, chromatographic profiles for the real sample analysis, specifications related to the method, and the corresponding color present in the GAPI pictogram (PDF)

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https://dx.doi.org/10.1021/acs.analchem.0c04663
Anal. Chem. 2021, 93, 1957−1961

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Author Contributions

A.T. and E.R. contributed equally to this work. M.L. and A.T. built the FPSM array device. F. Savini, S.R., F. Santavenere, and G.M.M. performed the FPSM array-LC-MS/MS analysis of EBA. All authors analyzed the resulting data. M.L., H.I.U., A.K., and K.G.F. designed the research and wrote the manuscript with the input from all other authors. The manuscript was written through contributions of all the authors that gave approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): E.B. is an employee at Eureka Lab Division. The other authors declare no conflict of interest.

■ ACKNOWLEDGMENTS

The authors thank MIUR ex 60%, "G. d'Annunzio" University of Chieti-Pescara (Italy), and the Department of Chemistry and Biochemistry, Florida International University for supporting the present work.

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