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Account & Perspective

Teflon Spray Ionization Mass Spectrometry

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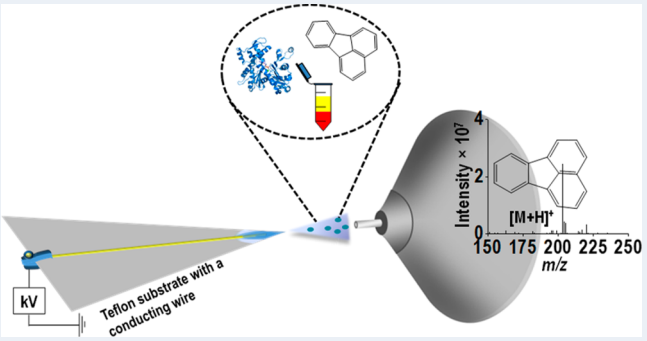
ABSTRACT: Polytetrafluoroethene, commonly known as Teflon, is a plastic famous for its inertness, strength, and nonstick properties, allowing its repeated use in many applications. We report the use of a triangularly cut Teflon substrate to take the place of paper in a form of spray mass spectrometry. A conducting wire (gold) at high potential (positive or negative) makes contact with a drop of the liquid sample at the apex of the triangle, causing a spray of droplets to be directed toward the heated inlet of a mass spectrometer. Saccharides, drugs, illegal additives, peptides, proteins, bilirubin, and vancomycin give mass spectra with high signal-to-noise (S/N) ratios, allowing detection at the nanogram per milliliter (ng/mL) level. Examination of each of these analytes demonstrates that Teflon spray is several orders of magnitude more sensitive than paper spray under the same conditions. Teflon spray ionization mass spectrometry is applied to the metabolomic and lipidomic profiling of biological fluid samples. Detection of polycyclic aromatic hydrocarbons is achieved with Teflon spray at 10 μg/mL concentrations. These experiments show the advantage of using Teflon over a normal paper substrate in detecting many environmentally and biologically relevant systems with high sensitivity and S/N ratio.



INTRODUCTION

Paper spray ionization, also simply called paper spray,[1] is a popular form of ambient ionization mass spectrometry in which a small volume of analyte, typically some biofluid, is deposited on the surface of a paper support and allowed to dry. Then solvent is added, high voltage is applied, and droplets from the sample are sprayed from the tip of the paper into a mass spectrometer. The origin of this technique might be traced to what Fenn called wick spray.[2] Paper spray ionization mass spectrometry was first introduced by Ouyang, Cooks, and co-workers,[3,4] who used filter paper as the spray substrate. It has since enjoyed much popularity, and applications and reviews may be found elsewhere.[5−8] Unlike the common way electrospray ionization is performed, paper spray requires no pneumatic assistance to transport analytes to the mass spectrometer inlet for chemical analysis. Because of its versatility and ease of operation, it has become an appealing form of ambient ionization mass spectrometry.

This spray method can be extended to a variety of substrates other than paper. One great advantage of paper spray is its capability of being a simple disposable substrate to hold the sample volume. But many molecular systems including proteins cannot be analyzed by this method, and the paper substrate cannot be reused repeatedly. There is reduction in the actual sample volume due to the absorbance properties of the paper substrate. In addition, the application of high voltage power to the paper substrate contributes to significant loss of sample during the analysis, as it can result in inherent oxidation of sample during the spray. Finally, it needs to be mentioned that filter paper is not totally clean and often contributes many unwanted peak artifacts to the recorded mass spectrum. In order to overcome these disadvantages, people have made a number of modifications to the paper spray ionization technique.

These modifications have helped immensely in overcoming the challenges arising from the physiochemical properties of paper substrate. Many additives have been tried on the paper medium for improving its performance, viz., carbon nanotubes,[9] silica gel,[10] urea,[11] nanoparticles,[12] metal organic framework materials,[13] waxes,[14] silanization,[15] and polystyrene microspheres.[16] Another approach was the chemical functionalization of the paper substrates for target enrichment and microextraction.[17−19]

A recent study in this field demonstrates the use of a glass slide,[20] an organosiloxane polymer,[21] or a conductive polymer[22] as a substrate for molecular ionization. This material replaces the paper substrate and aids in overcoming the disadvantages that result from the use of normal paper as an ionization source. The inherent dirtiness of the normal paper substrate and the subsequent complication in the mass spectra

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can be completely removed by performing paper spray in this way. Another advantage of this method is its capability to ionize complicated molecular systems, which are not possible with the normal paper spray method. Also, there is significant enhancement in the method performance, limit of detection, and sensitivity.

Development of new surfaces which overcome the limitations of the paper substrate in molecular ionization would be a welcome advance in spray mass spectrometry. In that sense, hydrophobic substrates would be a good choice to overcome the challenges like dead volume, contamination, and analyte adsorption. Also, hydrophobic substrates can hold sample solutions in microdroplet volumes without dispersion. All these factors inspired us to think of studying small droplet volume systems on hydrophobic substrates in the high voltage range. This produces mass spectrum with high S/N ratio in comparison with the normal paper spray ionization. The method can be applied to many biologically and environmentally relevant complicated systems, such as peptides and proteins, which are difficult to ionize with the normal paper spray ionization method.

In this study, we use Teflon as a substrate instead of paper for target analyte ionization. The Teflon substrate along with a conducting wire (for the application of high voltage) allows the emission of droplets from the sharp tip of the Teflon substrate cut in the form of a triangle. We apply this method for the analysis of various analytes in the low-to-high molecular weight range and compare Teflon spray with paper spray.

EXPERIMENTAL SECTION

All experiments were performed with triangularly cut Teflon sheets (of 1 mm thickness) and Whatman 42 filter paper, both of which were cut in a dimension of 15 × 25 mm (base × height). A narrow conducting wire (gold wire of length 3 cm and diameter 0.25 mm) was placed on the Teflon substrate, and it was connected with a high voltage power supply as shown in Figure 1A. This was held in front of the mass spectrometer (MS) inlet at a distance of 10 mm, and 10 μL samples (at concentrations ranging from 5 ng/mL to 10 μg/mL) were loaded at the tip of the substrate for each set of measurements. Mass analysis was achieved for all experiments using an LTQ Orbitrap Velos mass spectrometer (Thermo Fisher Scientific, San Jose, CA). The experimental conditions are solvents, acetonitrile (ACN), methanol/water (1:1), and hexane/methanol (1:1); mass spectrometer inlet capillary temperature, 275 °C; S-lens voltage, 55 V; and applied voltage from an external high voltage power supply, ±4.5 kV. All spectra were collected in positive- and negative-ion modes in the m/z 50−2000 mass range. Organic solvents, methanol, and ACN were provided by Fischer (Waltham MA) and hexane by Adamas-beta Reagent Co., Ltd. (Shanghai, China). Deionized water from Milli Q purification system (Millipore advantage A10) was used throughout the experiments. Fluorescein was purchased from Sigma-Aldrich (St. Louis, MO). Glucose, glucuronic acid, fucose, lactose, and glutathione were purchased from Aladdin Reagent (Shanghai) Co., Ltd. Gefitinib, imatinib, streptomycin, sunitinib, nilotinib, melamine, simvastatin, anthracene, fluoranthene, bilirubin, and vancomycin were brought from Adamas-beta Reagent Co., Ltd. Angiotensin II, lysozyme, and cytochrome c were provided by Sangon Biotech (Shanghai) Co., Ltd. Ibuprofen, indeno[1,2,3-*cd*]pyrene, and lidocaine were provided by Dr. Ehrenstorfer GmbH (Augsburg, Germany). Benzene and 1,2,3,5-tetramthylbenzene were from SCR Chemicals (Pty) Ltd. (Johannesburg, South Africa) and Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), respectively. Plasma was collected from the Vista mouse (Beijing Vital-Star Biotechnology Co., Ltd.). Saliva and urine samples were collected from a selected volunteer. These real samples were loaded on the substrate tip after sample pretreatment and dried before analysis. The collision induced dissociation (CID) technique was used for tandem mass spectrometry (MS^2 analysis).

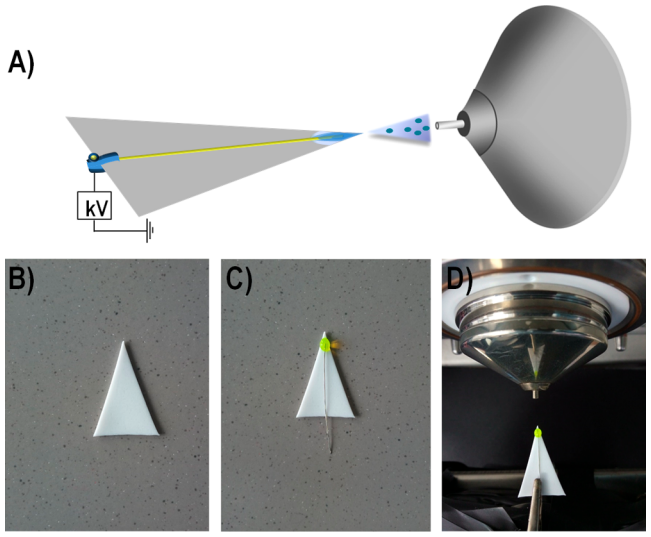

Figure 1. Teflon spray ionization mass spectrometry setup: (A) schematic representation and (B−D) photographs showing (B) a triangularly cut Teflon substrate of dimension 15 × 25 mm (base × height), (C) the same as (B) with a conducting wire (gold wire) and 10 μL of fluorescein solution (at the tip), and (D) the same as (B) connected with a high voltage power supply (through a copper clip) in front of the mass spectrometer inlet at a distance of 10 mm from it. A preliminary blank experiment was performed by comparing a full range (m/z 50-2000) mass spectrum of methanol/water (1:1) from the Teflon substrate with that from a paper substrate, both in the positive-ion mode. Note that the spray Taylor cone projects from the droplet surface in our Telfon spray ionization process.

RESULTS AND DISCUSSION

The traditional method of paper spray uses a triangularly cut paper substrate upon which the analyte solution is applied. Here, extraction and ionization of the target analyte (which is dispersed over the whole area of the paper) occurs from the sharp apex of the triangular paper substrate by application of

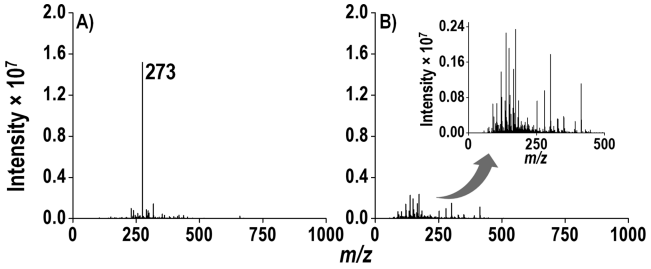

Figure 2. Full range mass spectra (blank) collected from a triangularly cut (A) Teflon and (B) paper substrates of the same dimension with 10 μL of methanol/water (1:1) at 4.5 kV in positive-ion mode. The expanded view of the noises from the paper substrate is shown in the inset of Figure 2B.

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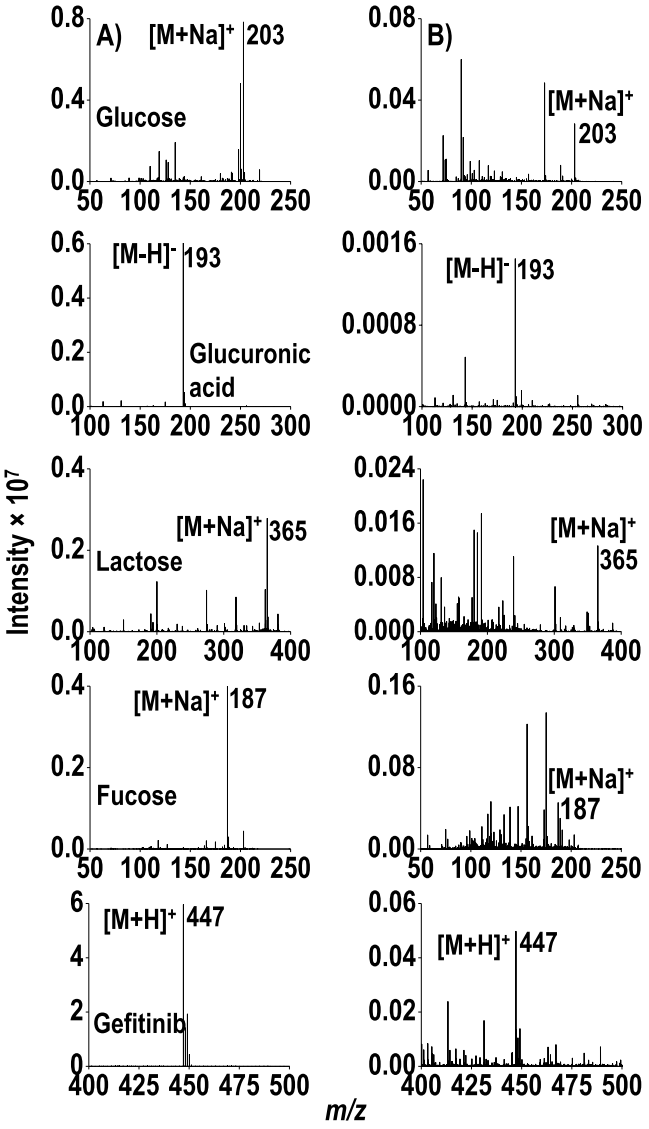

Figure 3. Mass spectra of different saccharides and drugs analyzed with (A) Teflon spray and (B) paper spray at +4.5 kV. All of the spectra are collected in positive-ion mode (except glucuronic acid), and detected analyte ions are labeled accordingly.

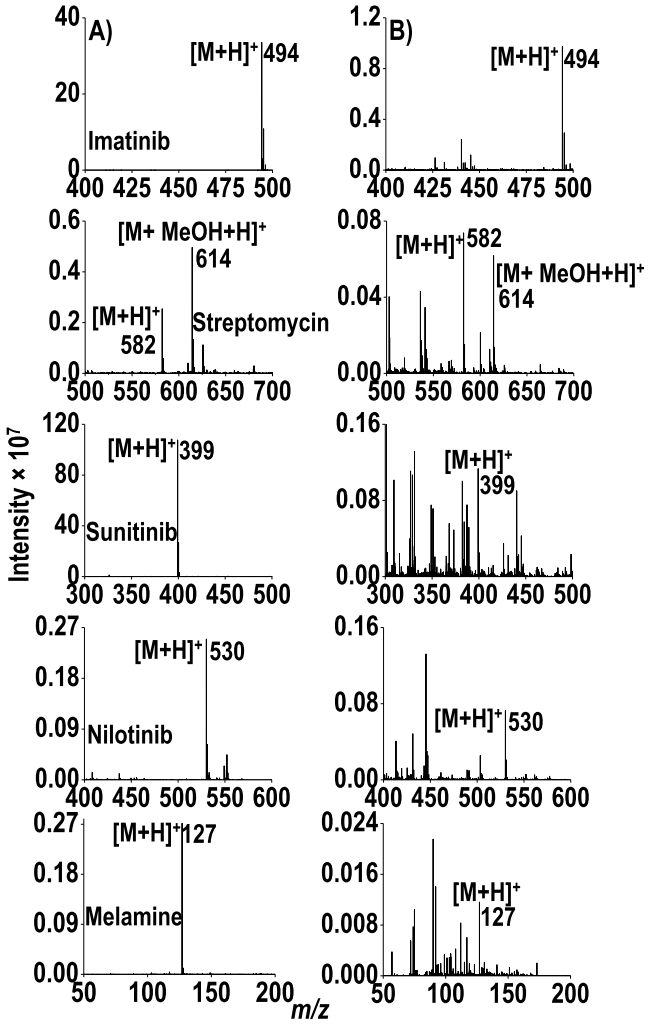

Figure 4. Mass spectra of different drugs and an illegal additive (melamine) analyzed with (A) Teflon spray and (B) paper spray at +4.5 kV. All the spectra are collected in the positive-ion mode, and analyte ion peaks are labeled accordingly.

high voltage on it. On the other hand, a hydrophobic substrate holds target analytes (in microliter volume) on its surface without dispersion, and it can be used for the study in real time of even a single droplet (of several microliters in volume). Whereas paper spray relies on the conductivity of the wet paper substrate, we introduce a thin conducting wire from the substrate base to the apex, which contacts the droplet. The experimental setup is shown in Figure 1. In this way, an electrical connection to the sample droplet is made by direct contact with the wire, and the spray of the target analyte occurs from the droplet on the substrate apex (loaded with 10 μL volume of analyte) by the application of high voltage to the wire. We chose Teflon as the substrate because of its hydrophobicity, strength, and inertness. Teflon was cut in a triangular shape (as shown in Figure 1B–D), and samples were loaded in microliter volumes at the apex. A narrow conducting metallic wire (gold wire) was put on its surface, and high voltage was applied through this wire which makes molecular ionization of a variety of analytes (in the low-to-high molecular weight range) from its apex with high sensitivity and high S/N ratios in the resulting mass spectra. Here, droplet spray occurs from the droplet surface, and a photograph that clearly shows the Taylor cone originating while applying the high voltage is presented as Figure S1.

Figure 1A represents the schematic diagram of the experimental setup which consists of a Teflon substrate with a conducting wire on it. The conducting wire is connected with an external high voltage power supply, and samples can be introduced at the tip of the substrate in microliter volumes (10 μL) with a pipet. The Teflon substrate tip was kept at a distance of 10 mm away from the MS inlet, and ±4.5 kV voltage was applied to the conducting wire from a high voltage power supply. The photographs of the experimental requirements are shown in Figure 1B–D.

In this experiment, a 10 μL volume of the solvent, methanol/water (1:1), was applied on both the Teflon and a normal Whatman 42 filter paper (with the same dimension as that of the Teflon substrate) and a voltage of ±4.5 kV was applied by keeping the substrate's tip at a distance of 10 mm from the MS inlet. The two spectra (with Teflon and Whatman 42 filter paper) are shown in Figure 2. The result clearly illustrates the surface cleanliness of the Teflon substrate

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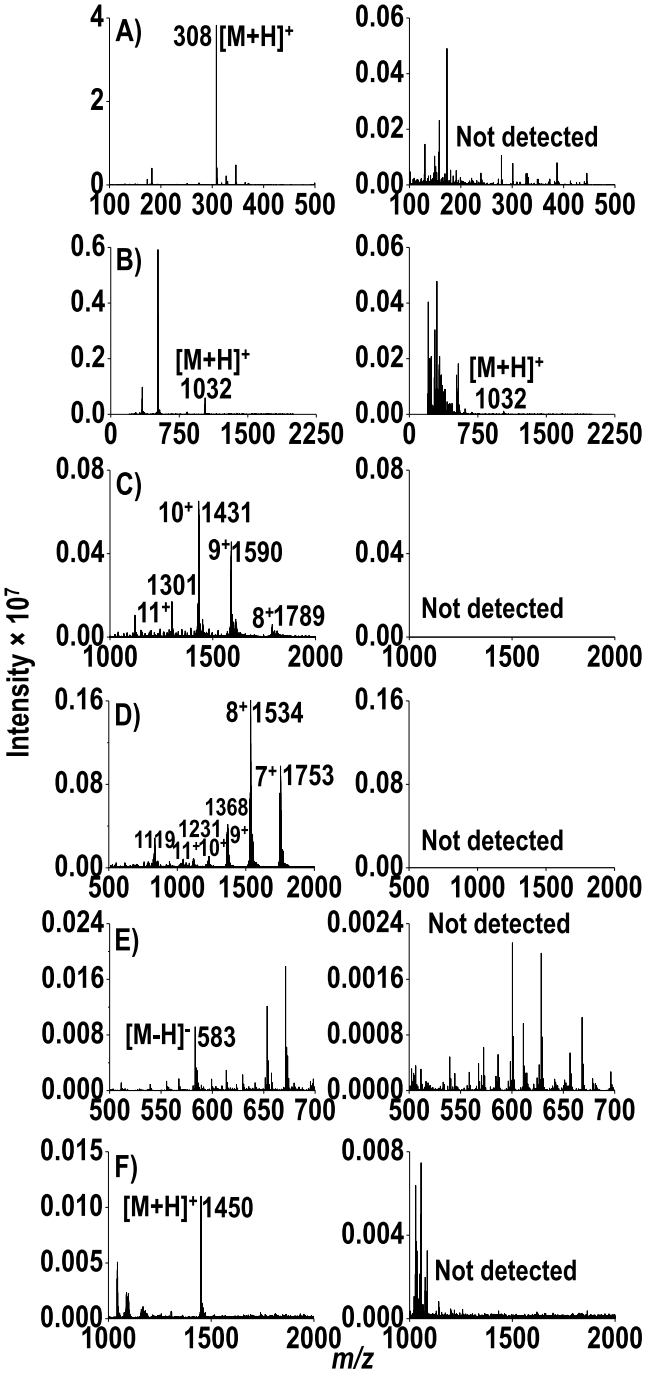

Figure 5. Mass spectra of (A) glutathione, (B) angiotensin II, (C) lysozyme, (D) cytochrome *c*, (E) bilirubin, and (F) vancomycin at 10 μg/mLconcentration collected with Teflon and paper spray (left and right panels, respectively). Spectra are collected in the positive- and negative-ion modes, and the detected analyte ion peaks are labeled accordingly.

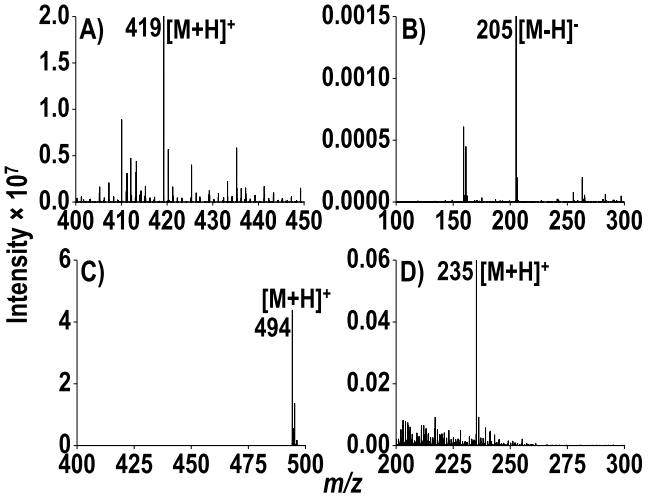

Figure 6. Mass spectra of (A) simvastatin, (B) ibuprofen, (C) imatinib, and (D) lidocaine collected with Teflon spray.

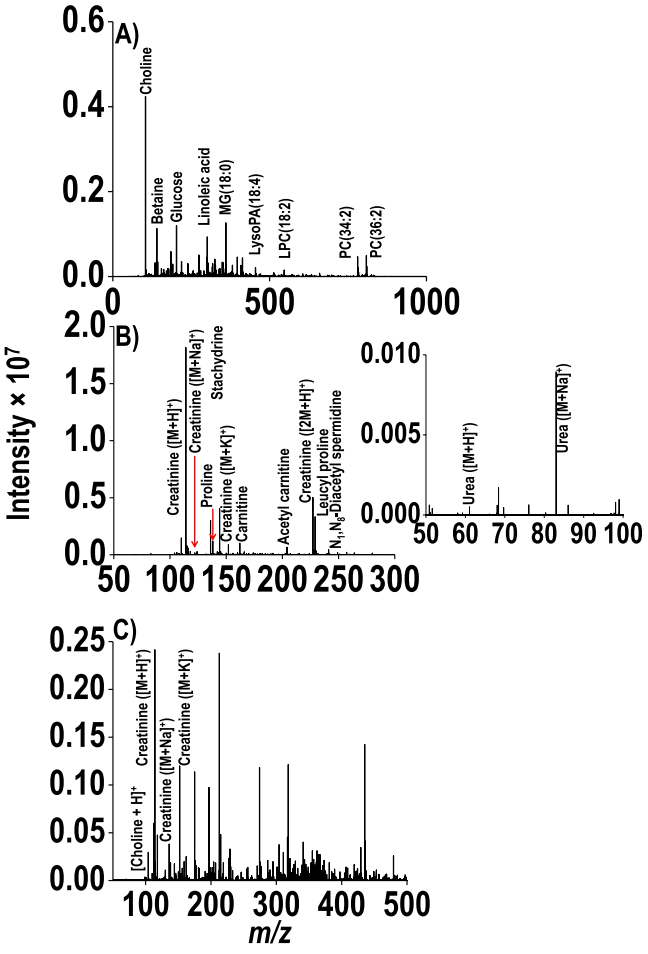

Figure 7. Mass spectra of dried (A) serum, (B) urine, and (C) saliva spots (at the tip of the Teflon substrate) collected after eluting the spot with methanol. The detected lipids and metabolites are indicated. An expanded view of the low mass spectrum collected from urine is also shown, which shows the presence of urea and its sodium adduct.

in comparison with the normal Whatman 42 paper substrate. The spectrum collected from the Teflon substrate is devoid of unwanted noise owing to its hydrophobicity and inertness.

The initial set of experiments was conducted with the selected biologically relevant analyte systems which include saccharides, drugs, and an illegal additive (melamine). These species were analyzed at 10 μg/mL concentration in respective solvents (methanol/water) from a Teflon substrate at ±4.5 kV. After that, the same set of analytes were detected with paper spray as comparison by keeping all the experimental parameters the same.

Figures 3 and 4 compare the mass spectra from the Teflon and paper substrates. The Teflon substrate showed an increase

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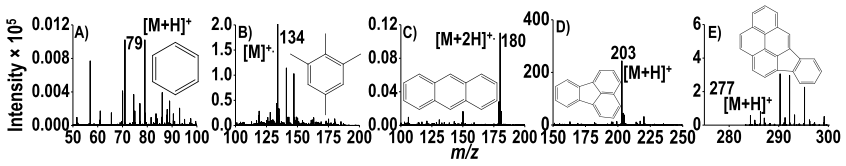

Figure 8. Mass spectra of (A) benzene, (B) 1,2,3,5-tetramethylbenzene, (C) anthracene, (D) fluoranthene, and (E) indeno[1,2,3-*cd*]pyrene detected with Teflon spray.

in the signal intensity by of several orders of magnitude (3.5×10^2 to infinity) compared to the paper substrate. In general, the mass spectra obtained from the Teflon substrate is devoid of many peaks which usually suppress the analyte ion signal intensity in normal paper spray ionization. The spectra obtained are clean with high S/N ratios compared to those obtained from the paper substrate.

This advantage of Teflon spray over normal paper spray in analyte ionization has been implemented in detecting many biologically relevant species which are not detectable or less sensitive when the paper substrate is used. This includes peptides and proteins, along with vancomycin (a high molecular weight antibiotic) and bilirubin (an orange-yellow pigment). The results are shown in Figure 5, which depicts the mass spectra of the above-mentioned species with Teflon as well as paper spray. The results emphasize the power of Teflon substrate in sensing molecular systems which are known to fail or give unacceptably low signals using conventional paper spray ionization mass spectrometry. A table listing the absolute signal intensities of these molecular systems with these two methods (Teflon and paper spray) is made available in Table S1.

In order to test the limit of detection (LOD) of Teflon spray, several pharmaceutical drug samples were prepared in methanol at ng/mL concentration (5−7 ng/mL) and analyzed in the positive and negative mode with Teflon as a substrate. The results are shown in the spectra (Figure 6) corresponding to simvastatin, ibuprofen, imatinib, and lidocaine. The detection of these drugs at the nanogram per milliliter level shows the high sensitivity of Teflon substrate in clinical applications. Additionally a calibration curve was obtained with these four analytes by varying their concentration in the nanomolar level with an internal standard (sunitinib) of known concentration and volume. The LOD calculation is detailed in the Supporting Information.

The applicability of this method has been demonstrated with some real-life samples. For that purpose, human serum, saliva, and urine were spotted on the tip of the Teflon substrate and dried. Supernatants of serum and saliva were spotted after protein precipitation with equal amount of methanol (100 μL of methanol was added to 100 μL of human blood and saliva followed with centrifugation at 10000 rpm for 10 min). Urine was spotted directly. After that, the dried spots (from serum, saliva, and urine) were eluted with methanol, and spectra were collected. Figure 7 shows the mass spectra for human serum, saliva, and urine in positive-ion mode. Mass spectra illustrate the presence of lipids from serum in the high molecular weight range and suggest the utility of this method for lipid profiling. Similarly, many representative metabolites were detected from saliva and are marked in the spectrum. Elution of the urine spot with methanol shows the presence of creatinine and its potassium adduct at m/z 114 and 152, respectively.

Detection of nonpolar polycyclic aromatic hydrocarbons (PAHs) is known to be challenging with normal methods of spray ionization as they lack functional groups for protonation or deprotonation. Here, Teflon spray has been implemented in detecting a variety of selected PAHs which are known to be toxic and carcinogenic. A set of PAHs had been made in hexane/methanol (1:1) solvent mixture at 10 μg/mL concentration and was applied directly on the tip of the Teflon substrate. Mass spectra are shown in Figure 8. Here, the spectra show protonated peaks corresponding to benzene, fluoranthene, and indeno[1,2,3-*cd*]pyrene. 1,2,3,5-Tetramethylbenzene was detected as a radical cation at m/z 134 and anthracene as $[M + 2H]^{+\bullet}$ at m/z 180. The identity of some of these species has been confirmed by MS^2 analysis, and the data are presented in Figure S10. The isotopic distribution patterns (theoretical as well as experimental) of these hydrocarbons are also shown in Figure S11, which also confirms the identity of these species.

The results show the potential of Teflon substrate as an ionization tool for the detection of PAHs which are difficult to carry out with normal paper spray ionization mass spectrometry.

CONCLUSIONS

The applicability of Teflon as the ambient ionization probe/substrate for a variety of analytes within a wide m/z range had been demonstrated. Background mass spectra collected from Teflon as well as Whatman 42 paper substrate clearly showed the superior cleanliness of Teflon over the paper. The use of an inert and hydrophobic Teflon substrate as an ionization probe has greatly reduced the adverse effects that occur in normal paper spray ionization mass spectrometry from its inherent dirtiness and hydrophilicity. The obtained results suggested the potential of Teflon in achieving high S/N ratios for a large variety of analytes within a wide m/z range. The results are helpful in detecting many analytes which usually get suppressed in normal paper spray ionization owing to unwanted noises resulting from their binding properties with paper cellulose. Different metabolites, drugs, illegal additives, peptides, and proteins were detected with Teflon spray, and the mass spectra were compared with traditional paper spray ionization mass spectrometry. The limit of detection (LOD) of Teflon spray with many pharmaceutical drugs has been achieved in the nanogram per milliliter level. These results show the capability of Teflon in extracting and ionizing drugs at low concentrations level with high sensitivity. The improvement in the extraction, desorption, and ionization efficiencies of Teflon over normal paper substrate clearly demonstrates its future possibility in detecting other drugs with high sensitivity. The application of Teflon spray in analyzing biological samples has been demonstrated with human serum, saliva, and urine. The results depicted the utility of Teflon in metabolomic or lipidomic profiling of biological fluids. Finally, the method had been implemented in detecting toxic and carcinogenic polycyclic aromatic hydrocarbons which clearly shows the advantage of this method over traditional electro-

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spray ionization method in detecting nonpolar hydrocarbons. Proton-transferred as well as electron-expelled analyte ions have been detected from a variety of PAHs under ambient experimental conditions. The results suggest the potential of Teflon spray in detecting environmentally relevant carcinogenic hydrocarbons which are not detectable with normal ionization strategies. The study could be extended for the characterization of PAHs in real environmental samples.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jasms.9b00069.

Photograph of the Tailor cone, (2) table depicting the signal intensities of various analytes with Teflon as well as paper spray, (3) LOD calculation, and (4) MS^2 spectra of different hydrocarbons and their isotopic distribution patterns (PDF)

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Notes

The authors declare no competing financial interest.

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