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Helium Conservation by Discontinuous Introduction in the Flowing Atmospheric-Pressure Afterglow Source for Ambient Desorption-Ionization Mass Spectrometry

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Abstract

As helium availability declines in many parts of the world and helium prices rise, it is desirable to limit helium use by plasma-based sources for ambient desorption-ionization mass spectrometry (ADI-MS). Here, helium flow to the flowing atmospheric-pressure afterglow (FAPA) source is interrupted to reduce total helium consumption. The FAPA glow discharge can be sustained for up to several minutes after the helium flow is halted, without damaging the source. As a result, a stable discharge can be maintained indefinitely by introducing relatively short periods of helium flow just before the discharge extinguishes. When helium flow is restored, the signal rises and reaches a steady state after 20 s; signal integration after this time yields mass spectra that are very similar, sensitivities that are 71% of those under continuous-flow conditions, and comparable precision.

Introduction

Ambient desorption ionization-mass spectrometry (ADI-MS) is powerful for qualitative characterization of a range of sample types, requires minimal sample preparation, and enables samples to be examined in their native state under ambient conditions.[1-3] Generally, ADI-MS sources can be broadly divided into three categories: 1) spray-based,[1] 2) laser-based,[4] and 3) plasma-based[3]. Several helium-plasma-based sources for ADI-MS have been studied extensively over the past decade and include direct analysis in real time (DART),[2] the low temperature plasma (LTP) probe,[5-7] and other dielectric barrier discharge (DBD) sources[8]. The flowing atmospheric-pressure afterglow (FAPA) is another helium-plasma-based ADI-MS source that offers attractive performance for a wide range of analyte and sample types,[3, 9] and is the subject of the present study. The pin-to-capillary design of the FAPA employs a negatively powered pin cathode and a capillary anode.[9] When helium flows through the discharge cell, a stable glow discharge is sustained and both charged and high-energy species flow out of the cell though the capillary in a stream heated by the plasma.[10, 11] This heated flow can desorb material from the surface of a solid or solution sample and energetic species from the plasma can ionize the resulting desorbed molecules.[11, 12] The region where heated gas and plasma species flow from the capillary anode is termed the "afterglow." When the sample, afterglow, and mass spectrometer inlet are positioned in near proximity, the mass spectrum of desorbed and ionized molecules from the sample surface can be recorded.

Because helium prices continue to rise globally and the reliability of its supply in some regions has faltered,[13] plasma-based ADI-MS ion sources that operate with helium as a support gas would benefit greatly from a reduction in helium consumption. Though seldom discussed, the DART source has used nitrogen as a standby gas to sustain the plasma between samples that are then interrogated with the source operated after helium flow is restarted.[14] However, this

DART source requires twice the helium flow rate than is typical for the FAPA source described here when helium flow is continuous and has the added complications of an additional gas supply and external heating elements.

There are several ways to reduce helium consumption with the FAPA source. The first is to alter the composition of the support gas, either by diluting the helium or replacing it altogether. Altering the gas composition would probably result in different high-energy species populations and would likely lead to different mass spectra. A past study that mixed hydrogen with helium for an ADI-MS source based on a dielectric barrier discharge found an enhancement with up to 0.9% H_2 in the plasma support gas, but proton transfer efficiency declined at higher concentrations of H_2.[15] To make a substantive impact on helium consumption a much larger portion of the discharge gas would need to replace He. If nitrogen were used as a more substantial constituent of the discharge gas, it would lower the concentration of helium excited-state species and also of He_2^+, which appear to be involved in the generation of other reactive species important for analyte ionization.[16]. A second tactic would be to reduce the flow rate of helium. However, a helium flow below the optimal range of 0.6 – 3.0 L/min results in a concurrent loss in signal due to reduced interaction between the plasma and the sample.[3, 9, 17] A third approach is examined here in which the helium flow is simply halted for a time and the flow restored only when a sample is to be analyzed or the discharge must be re-stabilized.

Experimental Methods

Pin-to-capillary FAPA-MS measurements. The pin-to-capillary FAPA was used in all experiments. The basic design has been described previously,[9] though materials and electrode spacing have been slightly modified in the version described here. The FAPA discharge cell is a quartz tube (9-mm i.d., 12-mm o.d.) that has been sealed around a centered pin cathode (arrowhead-shaped, tungsten) and a capillary anode (stainless steel, 2.5 cm long, 3.3-mm o.d., 1.5-mm i.d.). The electrodes are positioned 12 mm apart and the cell has a volume of approximately 3.2 cm^3. The source was powered by a glow discharge power supply (Model PTV3N200X, Spellman High Voltage Electronics, Hauppauge, NY) and current-limited to 30 mA. A potential of 88 V was applied to the capillary anode with a second DC power supply (Model E3621, Agilent Corporation, Santa Clara, CA) in order to eliminate any bias with respect to the voltage on the front plate of the mass spectrometer. To remove small amounts of tungsten oxide and tungsten nitride that appear on the cathode and anode after several days of continuous use, both the pin and the capillary were polished and sonicated in a nitric acid solution. Mass spectrometry measurements were performed with a time-of-flight mass spectrometer (Unique®, LECO Corporation, St. Joseph, MI) with minor modifications for improved handling of

the helium load; these alterations have been described elsewhere.[18,19] The FAPA source was oriented at a 45-degree angle with respect to both the sample and the mass spectrometer.[19]

Helium (99.999% purity, Airgas Mid America, Bowling Green, KY) flow rates ranged from 0.5 L/min to 1.5 L/min and were regulated by a mass-flow controller (MKS Instruments, Andover, MA). Except where otherwise noted, the flow rate was 0.75 L/min. A LabVIEW® program (Version 8.7, National Instruments, Austin, TX) was written to turn the helium flow on and off in a repeatable, automated manner with the mass flow controller so analytical and standby times could be selected conveniently.

Samples. Whole coffee beans (House Blend, Starbucks Corporation, Seattle, WA) were analyzed at the caffeine M+1 peak at *m/z* 195. Bupropion hydrochloride XL tablets (300 mg, BuPROPion, Actavis Inc, Dublin, Ireland) were characterized based upon the $M+1^+$ peak at *m/*z 240. Mass spectra were averaged over the entire length of the "analytical period" (see below) of a discontinuous flow experiment and compared to spectra obtained with continuous helium flow through the FAPA source. Acetone vapor was introduced from a stirred round-bottom flask containing acetone (AR® grade, Macron Fine Chemicals, Center Valley, PA) and connected via Tygon tubing to an outlet placed 1 mm from the capillary outlet of the FAPA source. All vapor issuing from this cell was from diffusion; no gas flow was employed. The protonated monomer peak of acetone at *m/z* 59 was used.

Sample introduction. Solid samples were held at a fixed location and moved in and out of the afterglow by means of a translational stage (model 12-5367.15, Semprex Corporation, Campbell, CA) with a range of 118.48 mm on the x-axis and 89.22 mm on the y-axis. The stage was controlled and automated with advanced stage motion control software (Amicron Software, Paderborn, Germany). Stage movements were synchronized and coordinated with helium flow as needed.

Infrared thermal imaging. Thermal images of the FAPA cell and a microscope slide inserted in the FAPA afterglow were obtained with a Fluke Ti40 FlexCam (Fluke Corporation, Everett, WA) infrared camera. Infrared (IR) images were taken at the end of periods both with and without He flow, to observe the extremes of temperature changes both in the FAPA cell and at the sample surface in the afterglow region. Images were analyzed with Fluke Smartview thermography software.

Sustained-discharge experiments. To characterize the behavior of the FAPA source when helium flow is halted, videos and photographs were taken with a digital single-lens reflex camera (EOS Rebel T4i, Canon USA, Melville, NY). The discharge was first powered continuously and then allowed to extinguish on its own when the level of residual helium in the cell became insufficient. Images were also obtained of the plasma restarting once helium flow was restored.

Results and Discussion

In this study, helium consumption is reduced in two ways. First, short periods of helium introduction (instead of a continuous flow) maintain the discharge indefinitely in a "standby" or "idling" mode between samples. This can be achieved with either a short shot of helium to stop the discharge from terminating (see Figure 1, frames B-E) or with a much lower total flow rate that sustains sufficient positive pressure to greatly limit diffusion of atmospheric gases into the discharge cell. In addition, steady helium flow is used only during a minimal sampling time, and without a major loss in sensitivity. This latter interval is termed the "analytical period" and is when sample analysis is performed and is displayed in Figure 1 in frames A and F. A diagram of the temporal operation as described in this report is illustrated in Figure S1 of the supplementary information.

Positive-pressure standby mode. When very low helium flow rates (approximately 0.01 L/min) are used when the primary gas flow is terminated, a small visible change in the plasma occurs, and the plasma quickly reaches a visibly stable state that can be sustained for up to 8 hours without interruption. Though it then takes some time to establish steady thermal characteristics, in instances where samples are evaluated very infrequently, this approach might provide acceptably stable plasma behavior and helium savings. Unfortunately, the discharge required nearly 10 minutes to reach a steady temperature in this mode of operation, which could result in relative imprecision in sampling due to very different thermal conditions in the source. This change in temperature takes place over several minutes without being countered by any source of cooling, which is disadvantageous compared to the "discontinuous standby mode" described below for the establishment of repeatable sampling conditions. Nevertheless, this mode of operation is being explored in greater detail and will be the subject of a future report.

Discontinuous standby mode. When the helium flow is turned off, the plasma is self-sustaining for one to three minutes, because of residual helium in the cell. In order to maintain the plasma, short periods of helium flow can be introduced intermittently to restore the helium composition of the cell. We have termed this operation of the FAPA with no helium flow "discontinuous standby mode." As helium diffuses from the cell and is replaced by air from the

ambient atmosphere, the plasma becomes less stable and slowly drifts away from the cathode, while the negative glow on the cathode surface declines in size; eventually, the plasma shuts down. When lower currents were used, the plasma was observed to shut down more quickly; below 15 mA, the plasma extinguishes nearly immediately. Therefore, a current of 30 mA was selected for the studies described here. This physical behavior is shown in the photographic sequence in Figure 1.

From Figure 1, as long as the discharge is not allowed to completely extinguish, the FAPA source returns smoothly to normal operation within 2 seconds after the He flow resumes. In contrast, if the discharge is allowed to terminate, it can be quickly reignited simply by restarting the He flow, but the first second or so appears more erratic (see video in SI), and the cell temperature drops rapidly during the period when there is no discharge. Overall, the most attractive approach for routine use appears to be to allow helium to flow for short periods (either 5 or 10 s) just before the discharge goes out; this operation enables the discharge to be maintained stably for indefinite periods, with only a fraction of the helium consumption of when the gas is flowing continuously. To demonstrate this standby mode of operation, the helium flow was turned on for ten seconds, and then turned off for one minute. This sequence was repeated for a period of over eight hours during which the discharge was sustained stably. This idling mode yields a savings in helium consumption by a factor of six.

If the discharge turns off and the cell is allowed to cool down, the system takes about ten minutes to warm up before it is stable once again. Maintenance of the discharge with short periods of helium flow keeps the plasma stable and eliminates the time and helium ordinarily required when the source is allowed to warm up and stabilize before a day of operation. Such a mode of operation keeps the discharge operating in a steady temperature range throughout the day. The following data pertain to experiments performed in this discontinuous standby mode.

Determination of optimal sampling period. When the helium flow is turned off, the discharge continues for a time, as described above, but the flowing afterglow (outside the cell) immediately disappears; as a result, the mass spectrum also vanishes. Though some ions are produced in the discharge, no substantial gas flow is present to warm the sample and thermally desorb analytes and the population of high-energy species that can diffuse from the weakened plasma into the open atmosphere in the absence of such a gas flow must fall severely. The sudden disappearance of ion signal in the mass spectrum suggests the importance of a gas flow in facilitating the transport of analyte ions to the mass spectrometer – the instrument's vacuum system alone might not be sufficient for this purpose. Recent ADI-MS experiments in our group[20] and by others[21] has explored these transport phenomena in greater depth, but more work is

needed to fully decouple the forces of the gas flow and the vacuum of the instrument. In contrast, when the helium flow is restored, it takes a finite time for a solid sample to be heated and for atmospheric constituents (those that have diffused into the cell in the absence of gas flow) to be expelled from the FAPA cell and for normal ionization and gas-flow conditions to be reestablished. The gases that diffuse into the cell are probably responsible for formation of a noticeable oxide or nitride layer on the surface of the tungsten pin electrode. Although no loss in performance has been observed due to this modification of the electrode surface, regular polishing of the electrode is advisable once the change is visually observed.

The time necessary to reconstitute the gas in the discharge cell with 99% helium was calculated to be 2.2 s. To determine this value, the discharge cell was modeled as an exponential-dilution chamber with dimensions used in these experiments and assumed initially to have no appreciable helium present. When helium flow is restored at a flow rate of 0.75 L/min, the composition of the cell was iteratively calculated based on the composition of the gas both entering and exiting the cell. Of course, if the discharge is operating in standby mode (in which the plasma is maintained), helium will still be a major constituent of the gas in the cell and the washout time should be shorter. However, the experimental approach to a steady signal is much slower than this simple analysis would predict and suggests that sample heating is an important factor. (*cf*. Figure 2). Here, acetone vapor was introduced into the afterglow at the exit of the FAPA source to distinguish thermal desorption from ionization. The green trace in Figure 2 shows a strong MS signal from acetone as soon as He flow is restored to the discharge. After some fluctuation that is likely related to the establishment of a steady He flow pattern,[22] a stable signal is established (within 10 s). Further work with vapor samples and discontinuous He flow is currently underway to explore these phenomena in greater depth.

Because desorption is largely a thermal process,[23] the signal from a solid sample understandably reaches a relatively steady value more slowly, and takes approximately 20 s, a period that is largely independent of He flow rate (*cf*. Fig. 2). To clarify this point, the thermal behavior of the sample was explored with IR thermography, which revealed lower sample temperatures when the helium flow was on for less than 20 s, and little change in sample temperature when longer periods of helium flow are used.

Thermal characterization of FAPA cell. Infrared photography was utilized to characterize discharge cell and sample temperatures (*cf*. Figure 3). Thermal characteristics were found to be dependent upon the duration of both the analysis and standby modes. Extended standby times (with no He flow) result in a hotter cell; however, once helium flow is resumed, the cell temperature drops by approximately 35°C over a period of 30 s. This behavior necessitates several

helium on-and-off cycles before a steady temperature is achieved, with the time necessary to reach this temperature increasing with standby time. The thermal images in Figure 3 were obtained after the temperature has stabilized. Temperatures for the sample when He flow is absent are largely independent of the length of the analytical operation of the source, provided there is enough time in standby mode to cool the surface (15 s is sufficient). The sample is heated throughout the period when He flows, though much of this behavior (a rise of 10°C) occurs in the first 5 s after the helium flow is restored (not shown in Fig. 3). This rapid initial heating is probably because the gases that had been heated during standby mode are expelled onto the sample in the first 5 s. These data are consistent with the behavior of the caffeine signal in Figure 2, where the most rapid rise in the MS signal occurs in the first 5 s, though the signal continues to approach stability for nearly 15 s more. Due to the lack of thermal equilibrium, the temperatures expressed here for the FAPA cell should be viewed as relative values.

Effect on sample temperature. Analyte desorption by the FAPA source, as with many other plasma-based systems, occurs via thermal desorption.[23-25] Accordingly, discontinuous helium flow affects the sample temperature and results in changes in sensitivity. The maximum sample temperature for analysis times shorter than 20 s is lower than for longer times. In contrast, although the cell temperature rises with standby time, the sample temperature is not affected, and no significant change in the signal occurs. However, although sample temperature for different standby times (10, 30 and 60 s) remains the same (~90°C), sample temperatures with constant He flow are lower (~80°C). Thus, discontinuous helium flow is likely to assist thermal desorption for less volatile analytes. The extent of sample heating and cooling depends on several additional factors including ambient conditions, plasma power, sample composition, and sample location relative to the capillary outlet of the FAPA source.

Mass spectral consistency. It is possible that using interrupted helium flow with the FAPA source could result in time-varying mass spectra caused by changes in populations of reagent-ion species or in the thermal fragmentation of analyte species. To evaluate this potential problem, two analytes were explored. Figure 4 shows the temporal behavior of peaks in the bupropion mass spectrum during a 20-s period of helium flow after the flow had been interrupted for 30 s. Bupropion, a common anti-depressant, was selected because both its molecular ion and a fragment ion are prominent (cf. Figure 4A). To clearly demonstrate the difference in the extent of each type of signal in Figure 4B, the percent of all peaks is plotted as a function of time rather than plotting the absolute signal levels, which rise throughout most of the 20-s sampling period shown, as demonstrated in Figure 2. In Figure 4B, peaks from the dominant fragment ion (*m/z* 184-187) and the protonated molecular ion (*m/z* 240-242) rise gradually whereas the peaks at m/z 166-170 decline slowly. The latter peaks exhibit a different isotope distribution from the peaks at *m/z* 184-187 and 240-242 and are

probably not fragments of bupropion but rather are background peaks, which can change in the laboratory from day to day. The same background peaks were observed in mass spectra of several types of samples that were examined on the same day these data were obtained. In Figure 4B, the green line represents the sum of all peaks other than those due to bupropion. The flatness of this line indicates that ionization efficiency remains constant during the run. The consistency of peaks in the mass spectrum throughout the period of helium flow and the lack of background during the period without helium flow indicate that integration across an entire period of He flow (or multiple consecutive periods) would not significantly diminish precision.

As shown in Figure 5, mass spectra from a coffee bean sample are identical when obtained with either continuous or discontinuous helium flow. This similarity indicates that spectra should be consistent with those obtained in past investigations with the FAPA source; also similar analytes should be observable with both operational approaches. Overall, the similarity in spectra suggests a high probability of similar desorption, fragmentation, and ionization mechanisms.

Sensitivity and Precision. The sensitivity and precision of the discontinuous flow method were compared to those of continuous-flow operation. A coffee bean was placed in front of the FAPA source with continuous helium flow for 20 s, and then moved away. The FAPA was then switched to operate discontinuously by terminating the He flow for 30 s, then moving the sample back into place before restarting He flow for 20 s with the same sample. The process was repeated ten times and the signals compared. Five of these cycles are shown in Figure 6. After adjusting for slight differences in the sampling period and placement between the two approaches, the signal for the discontinuous technique was 71% of that from the continuous method. This lowered sensitivity with discontinuous flow was found to be statistically significant (P-value <0.0001) and arises because some of the 20 s of helium flow is spent purging nitrogen from the discharge cell and heating the sample, so the actual measurement time is somewhat shorter. It is during these periods when the signal is rising at the beginning of each discontinuous sampling period that the most erratic signals are observed in Figure 6 (see also Figure 2), accounting for the slight loss in precision.

These small losses in sensitivity and precision are considered to be acceptable when one considers the substantial reduction in helium consumption that accrues from using discontinuous helium flow. In the example of Figure 6, the helium savings would be in excess of 50%, though helium use could be more dramatically reduced depending upon the frequency with which a sample analysis is needed. Of course, for applications with higher required analysis frequency, this advantage would likely be less significant.

Comparison to previous approaches for helium savings in ADI-MS. Though previous approaches to reduce helium consumption have been implemented for the DART source, the practical impact of such a standby operation has not been explored in any depth. Here, plasma behavior and analytical performance have been described in a method with less instrumental complexity (e.g. no gas flows need be switched). The method described here demonstrates a considerable practical advantage of the pin-to-capillary source design over other plasma-based ADI-MS sources. These results should not be presumed applicable to the lower-current DART source, nor should our new approach be expected to work as well with other designs of the FAPA source. Accordingly, future plasma-based ADI-MS sources should be devised with an awareness of the practical implications of source designs that limit the applicability of helium conservation techniques such as those describe here. The pin-to-capillary FAPA geometry was able to sustain the plasma much longer than other iterations of the FAPA source (including the original pin-to-plate version and the concentric halo-FAPA). The higher currents used for the FAPA appear to be important for maintaining the plasma in the absence of a flowing helium stream, and the use of a capillary as the exit orifice greatly reduces the rate of atmospheric diffusion into the region in which the plasma is sustained.

Conclusions

Discontinuous helium flow in FAPA-MS reduces helium usage with minimal sacrifice in performance. A FAPA discharge can be maintained for one to three minutes after helium flow is stopped. By restoring helium flow before the discharge terminates, it is possible to maintain the discharge over long periods while consuming only a small fraction of the helium required by operating the FAPA with continuous helium flow. Maintenance of the discharge in this standby mode eliminates the stabilization period necessary after a discharge is ignited, which keeps the system ready for immediate use as needed. After He flow is restored, signals from solid samples rise for the first 20 s and then remain constant for extended periods for all flow rates tested. This rise time is due to warming of the sample surface. Changing the duration of the standby time was found not to have a significant effect on signal magnitude, precision, or sample temperature. Signals from a sample analyzed with 20 s of restored helium flow were 71% of those obtained with a 20-s exposure of a sample to a continuously flowing FAPA. Use of longer signal-integration times would provide even more similar performance between the continuous and discontinuous modes of operation, since the sensitivity beyond the first 20 s of helium flow is not changed. Of course, longer analysis periods will consume more helium and time; in many applications with easily detected and higher-concentration analytes, this tradeoff would not be necessary. In addition to decreased helium consumption, discontinuous helium flow has the advantage of more

limited helium flux, which should allow the source to be used for mass spectrometry without instrumental modifications that most helium plasma-based ADI-MS sources require.

The results described here should be expected to be applicable only to the pin-to-capillary version of the FAPA source. Although some dimensions and materials might change between otherwise similar versions of the source, common features, such as a conductive capillary and a small orifice that retard diffusion and higher currents than some other sources (such as DART) use, enable the behavior and performance characteristics described here. Accordingly, the ability to conserve helium with discontinuous gas flow could be an advantage of the FAPA source in ADI-MS.

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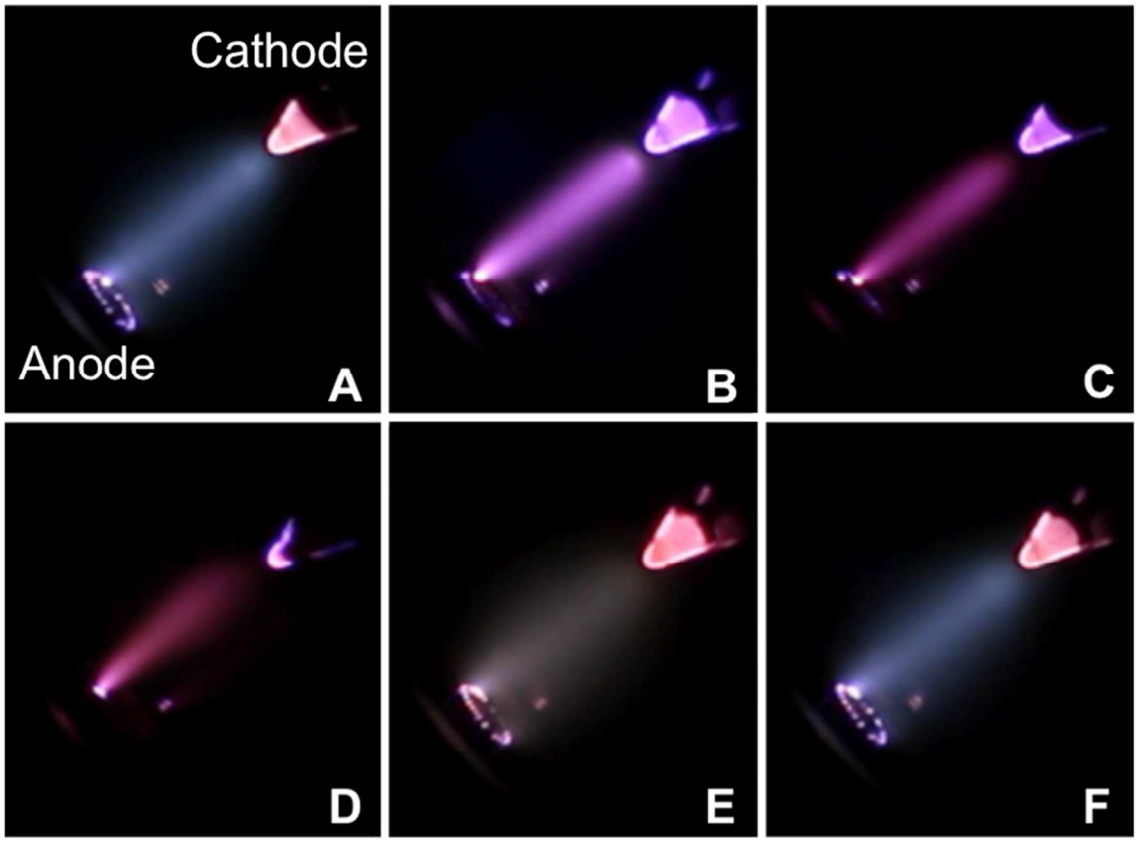

Figure 1: Temporal progression of discharge appearance after He flow into the FAPA cell is turned off. A) Plasma with 1 L/min continuous He flow, B) 5 s after He flow is turned off, C) one minute after He flow is turned off, D) two minutes after He flow is turned off, E) appearance when He flow has been reestablished for 0.5 s after plasma had shut down for 1 s F) Return to normal operation 2 s after He flow reestablished. This sequence is shown in video format in the supplementary information.

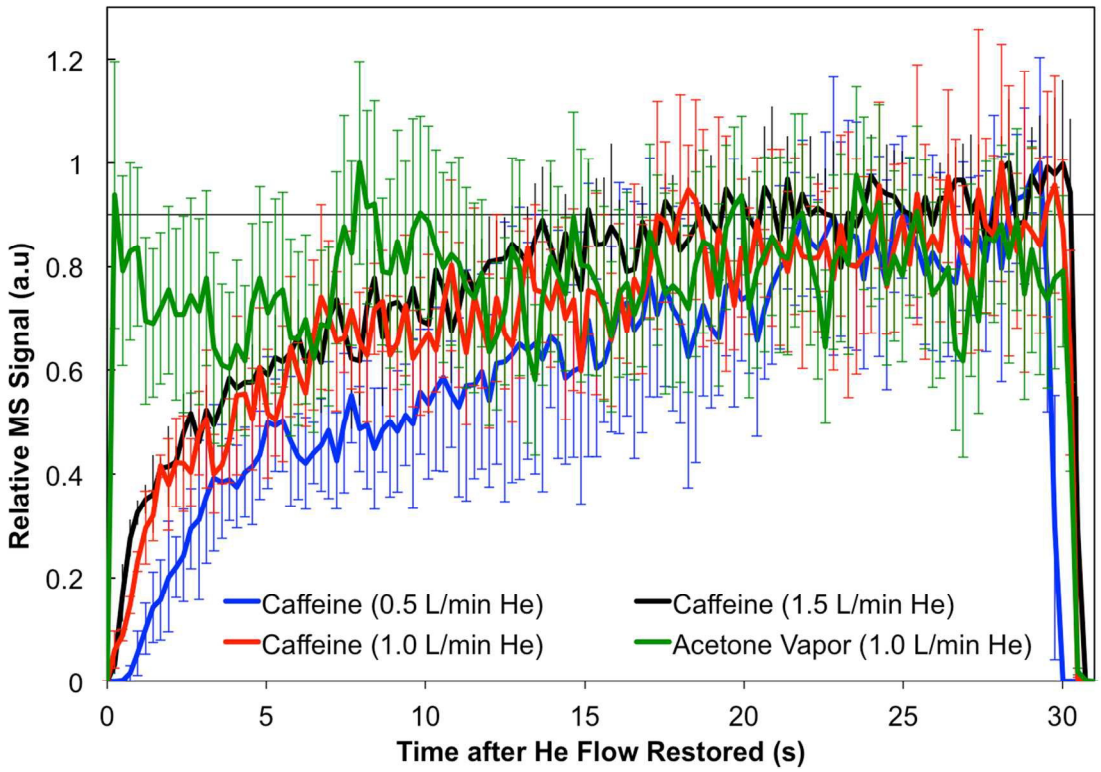

Figure 2: Mass spectrometric signal of a caffeine peak at *m/z* 195 and a peak from acetone vapor at *m/z* 59 as a function of time after He flow is restored for 30-s analysis times at different He flow rates. The horizontal line represents a value equivalent to 90% of the maximum value for each trace. Traces shown here were obtained after 15-s standby periods before each measurement. The error bars represent the standard deviation for each time point from 5 separate sampling periods that were normalized to the maximum averaged signal.

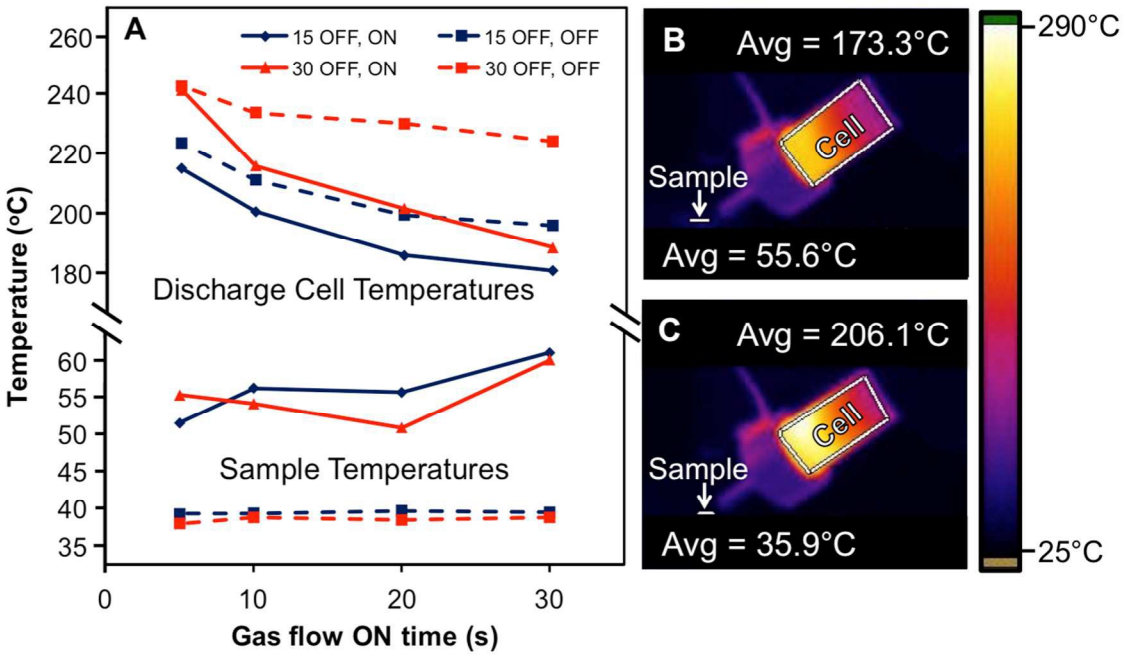

Figure 3: Thermal characterization of the FAPA cell and sample. A) "On" temperatures (when He is flowing, solid lines) and "off" temperatures (when He is not flowing, dotted lines) were measured for both the discharge cell (top traces) and microscope slide (bottom traces). All measurements were made at the end of a period during which He flow was on or off; labels indicate the period during which He flow was turned off before flow was restored and the last part of each label indicates whether the measurement was made with He flow on or off (*e.g.* "15 OFF, ON" indicates that the He flow was turned off for 15 s between periods of flow and the measurement was taken at the end of a period during which the He flow was on). When the helium flow is on (B), it cools the discharge cell, but carries a heated stream of air onto the slide; when the flow is turned off (C), the cell gets hotter and the sample drops in temperature. The images in B and C represent behavior for 15-s standby times. The top temperature in each image is the mean of all pixels inside the white box labeled "Cell" and the bottom temperature is the average of all pixels along the line labeled "Sample". Temperature values shown here have been corrected for the emissivity of the quartz cell (0.93) and glass slide (0.92).

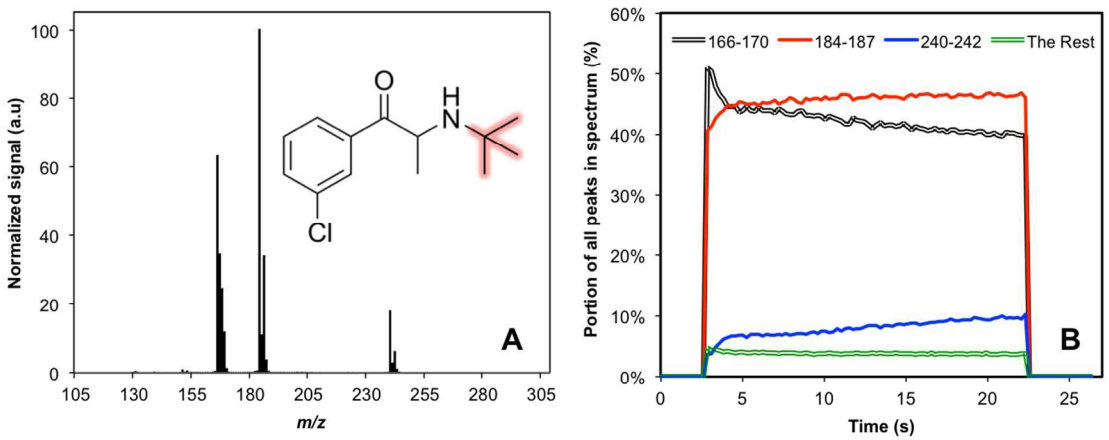

Figure 4: Mass-spectral consistency over the course of 20-s helium flow with a bupropion sample. A 30-s standby time preceded the restoration of helium flow. A) Bupropion structure and its mass spectrum integrated over the 20-s analysis period. The highlighted t-butyl group is lost in the peaks at *m/z* 184-187 and the protonated molecular bupropion ion is comprised of peaks with *m/z* 240-242. The other major group of peaks in the mass spectrum is at *m/z* 166-170, which are background peaks commonly observed in FAPA mass spectra. B) Temporal behavior of major groups of peaks throughout the analysis period. The green line is the integral value of all peaks other than those in the FAPA background.

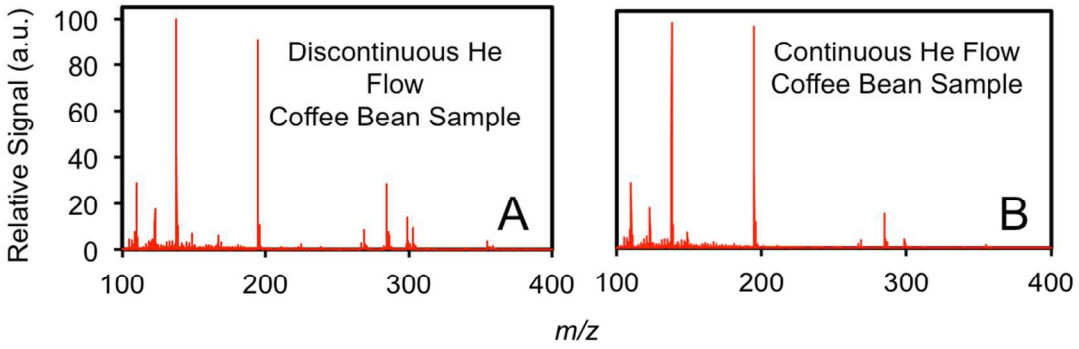

Figure 5. Comparison of mass spectra of a coffee bean sample for continuous and discontinuous helium flow experiments. A) Background-subtracted mass spectrum of coffee bean sample with discontinuous helium flow after the helium flow is interrupted for 30 s and restored for 20 s. B) Background-subtracted mass spectrum of coffee bean sample with continuous helium flow (20 s integration). Mass spectra are normalized to the largest peak in each spectrum.

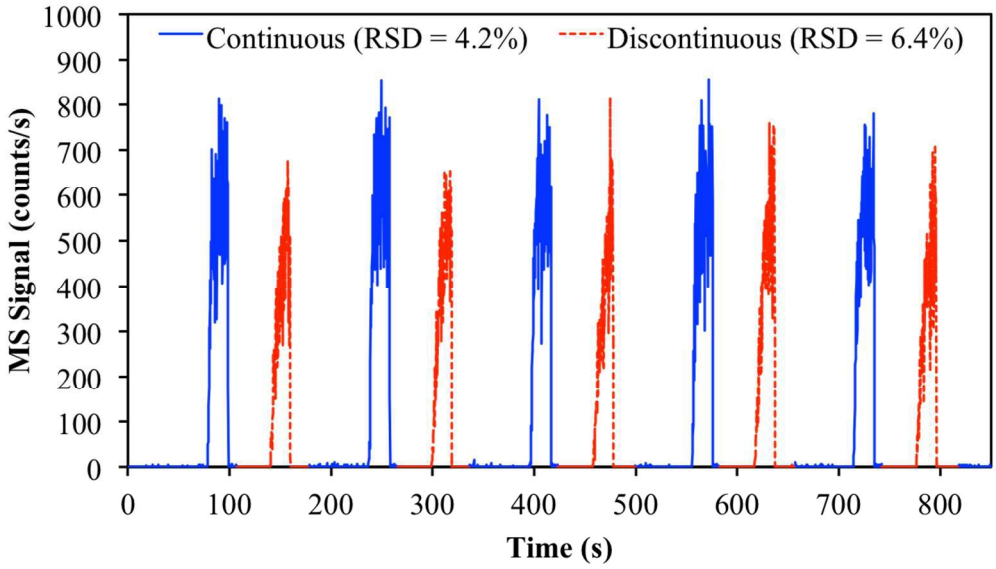

Figure 6. Signals for caffeine (*m/z* 195) measured during continuous (blue) and discontinuous (red) He flow. Continuous-flow experiments include the introduction and later withdrawal of a sample from the MS sampling area. Relative standard deviation (RSD) values indicate precision of integrated sampling periods.