International Journal of Mass Spectrometry 312 (2012) 201–207

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

Paper spray ionization devices for direct, biomedical analysis using mass spectrometry

Qian Yang[a], He Wang[a], Jeffrey D. Maas[b], William J. Chappell[b], Nicholas E. Manicke[c], R. Graham Cooks[c,d,*], Zheng Ouyang[a,d,**]

[a] Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA
[b] Department of Electrical and Computer Engineering, Purdue University, West Lafayette, IN 47907, USA
[c] Department of Chemistry, Purdue University, West Lafayette, IN 47907, West Lafayette, IN 47907, USA
[d] Center for Analytical Instrumentation Development, Purdue University, West Lafayette, IN 47907, USA

ARTICLE INFO

Article history:
Received 1 March 2011
Received in revised form 22 May 2011
Accepted 24 May 2011
Available online 1 June 2011

Keywords:
Clinical analysis
Ambient ionization
Electrophoresis
Paper spray
In situ analysis

ABSTRACT

Paper spray ionization has been developed as a direct, fast and low-cost sampling and ionization method for qualitative and quantitative mass spectrometric (MS) analysis of complex mixtures. Analyte ions are generated by applying a high voltage and a small volume (~10 μL) of spray solvent onto a porous substrate. The sample can be preloaded onto the paper or mixed into the spray solution. The geometry of the paper and the method of supplying the necessary internal standard are important factors that affect the ionization efficiency and subsequently the sensitivity and quantitation accuracy of the analytical data. As the cut angle of the paper tip is changed, the spray plume, the total spray current and the electric field intensity at the tip all vary correspondingly, with resulting differences in signal intensity. Sample load is another important factor for obtaining a stable MS signal and accurate quantitative results. The optimal sample load was found to be dependent on the paper size. The dissolution and spray process was also investigated and analyte transfer on paper was shown to be largely associated with bulk solution flow toward the spray tip. The information gathered from these systematic studies provides guidance for the design and optimization of a disposable sample cartridge for paper spray MS, a device which potentially is suitable for fast clinical analysis, especially for point-of-care diagnostics.

1. Introduction

Mass spectrometry (MS) is a powerful method for analyzing complex mixtures, especially when augmented by tandem mass spectrometry (MS/MS). The development of electrospray ionization (ESI) [1] and atmospheric pressure chemical ionization (APCI) [2], allowed the techniques of liquid chromatography (LC) and MS to be combined to form a relatively robust and highly practicable method that is now widely used [3]. The LC/MS and LC/MS/MS methods are currently used for quantitative and qualitative analysis for pharmaceutical and clinical applications as well as for biological studies. Particular areas of application include (i) therapeutic drug monitoring (TDM) [4,5], for example, for treatments involving immunosuppressants, antiretrovirals, and antidepressants; (ii) newborn screening for inborn errors of metabolism [6,7], such as fatty acid oxidation disorders or aminoacidopathies; (iii) forensic and clinical toxicology [8] and (iv) proteomics [9]. Although there are many well-established analytical methods for detecting biomarkers in serum and tissue utilizing antibody-based detection methods such as enzyme-linked immunosorbent assay (ELISA), development of robust antibody reagents for specific biomarkers is difficult and time-consuming [10]. In comparison with these biochemical or immunological analytical technologies, the major advantages of MS in clinical applications include the speed of analysis, the high specificity, especially for mixtures, the low limit of detection (LOD), and lack of any requirement for analyte-specific reagents (ASRs) [11]. All of these factors make MS a versatile tool for rapid and high-throughput analysis.

Currently MS analysis provides significant amounts of information about complex samples, but the use of MS systems in routine clinical laboratories could be increased significantly if some current limitations could be removed. One bottleneck is the complexity of the required sample pretreatment before MS analysis, which typically involves labor-intensive and time-consuming sample manipulations including extraction, purification and chromatographic separation. Another limitation is the expertise required for

* Corresponding author at: Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, USA. Tel.: +1 765 494 5263; fax: +1 765 494 9421.
** Corresponding author at: Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA. Tel.: +1 765 494 2214; fax: +1 765 496 1912.
E-mail addresses: cooks@purdue.edu (R.G. Cooks), ouyang@purdue.edu (Z. Ouyang).

1387-3806/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijms.2011.05.013

MS operation and data interpretation. Widespread use of MS for pharmaceutical and clinical applications is likely to result from the availability of more user-friendly MS analytical systems.

The emergence of a new family of ionization techniques, the ambient ionization methods [12], addresses this need. These methods include desorption electrospray ionization (DESI) [13], direct analysis in real time (DART) [14] and many others [15–17]. These methods have simplified MS analysis by allowing the generation of analyte ions directly from ordinary samples under ambient conditions without sample preparation or prior separation steps. The barriers to MS analysis of samples in their native states are being overcome by these strategies. Many groups have reported encouraging results in the direct analysis by various ambient ionization methods of pharmaceutical drugs [18–24], illicit chemicals [25–31] and biological molecules in complex matrices [32–36].

As a new branch of the ambient ionization, the recently developed method of paper spray ionization (PS) has been shown to have some promising features and a wide range of applications [37–41]. The capability of paper spray for direct analysis of crude biological samples has been demonstrated with urine [38], dried blood spots (DBS) [40], whole blood [37], and tissue samples [41], all of which are highly important for clinical applications. Numerous drugs in dried blood spots, including dextrorphan, amitriptyline, imipramine, citalopram, and imatinib, have been directly analyzed from paper substrates using paper spray. This demonstrated that paper spray can be used as an effective alternative to standard extraction procedures [42] and also to newer methods including DESI [43] and liquid microjunction surface sampling probes (LMJ-SSP) [44]. Linear responses for these drugs were recorded by PS-MS across a concentration range of at least three orders of magnitude, fully covering their therapeutic ranges [39]. Limits of quantitation for each of these drugs were around 1 ng/mL in whole blood [39]. Various methods for applying internal standard (IS) have been investigated, including printing the paper with the IS before loading the blood sample, soaking a punched out section of a DBS with the IS, and using a spray solvent containing the IS [40].

In this paper, a systematic characterization of paper spray devices was conducted. Several factors, including the geometry of the paper triangle and the sample loading, were shown to have an impact on the ionization efficiency of paper spray. The concept of making paper spray disposable sample cartridges has also been implemented based on the knowledge acquired from the characterization study.

2. Experimental

Chromatography paper used for paper spray was purchased from Whatman (Whatman International Ltd., Maidstone, England). Bovine whole blood (with sodium citrate as anticoagulant) was purchased from Innovative Research (Novi, MI). All other reagents were purchased from Sigma–Aldrich (Milwaukee, WI) and used without further purification. Methanol/water solution (1:1, v/v) was used as the solvent for paper spray unless otherwise noted. Mass analysis was performed using a Thermo Fisher LTQ mass spectrometer (Thermo Fisher Scientific Inc., San Jose, CA). The temperature of the MS capillary inlet was typically set at 150 °C and the tube lens voltage was set at 65 V. Tandem mass spectra were recorded using collision-induced dissociation (CID) and product ion scans were recorded. The voltage used for paper spray ionization was 4.5 kV in positive mode, unless otherwise noted.

3. Results and discussion

This study sought to achieve a systematic characterization of the paper spray mass spectrometry experiment and the effects of physical variables on its analytical performance. The geometry, structures and materials of the substrate and the operating parameters of the paper spray were all investigated. The first observation made was that spray only occurs at sharp tips at the paper edge, such as the four corners of a square. The spray could be eliminated from one or more points by rounding the corners (Fig. 1a). The angle of the paper tips plays a key role in the generation of the spray. To investigate the effect of tip angle in paper spray, paper substrates with a variety of shapes were designed and cut precisely using a laser as shown in Fig. 1b. Each shape consisted of two parts: a tiny salient with one of the five different angles (30°, 60°, 90°, 120° and 150°) in the front and an identical large circular part behind it. It was found that the spray occurred only at the salient. The area of the circular part was constant for all the shapes and was much larger than the salient area to ensure that the solvent evaporation process was comparable for each design. Accordingly, the difference in MS signal observed with these substrates was mainly due to the differences in tip angle.

A cocaine solution of 15 μL volume (1 μg/mL in methanol/water, 1:1, v/v) was applied to each paper substrate, and the shape of spray plume, the abundance of the protonated cocaine ion (*m*/*z* 304) and the total spray current were recorded (Fig. 1d). The diameter of the spray plume was observed to decrease as the angle increased, thus and a larger proportion of the charged droplets population was directed into the MS inlet (Fig. 1c). However, no spray could be observed for the tip with an angle 150°. Moreover, the tolerance of the signal to the positioning of the paper became smaller with larger angles and the larger the angle, the shorter the critical distance needed to produce the spray. It is interesting that the change in peak intensity of the cocaine fragment ion *m*/*z* 182 with angle is not monotonic (Fig. 1e). The same behavior is observed for the protonated molecule, *m*/*z* 303 although the total ion current intensity steadily increased for 30–90° and then decreased. The onset voltage for paper spray increased continuously as the angle was increased. It was 3 kV for tips with a 30° and 60° angle and increased to 4 kV for tips with angle 90° and 120°. At spray voltages exceeding 6 kV, severe corona discharge occurred.

The total current increased as the spray voltage increased and the 30° tip always gave the highest current (Fig. 1f). The electric field at the spray tip was numerically calculated using the finite element analysis tool COMSOL Multiphysics 4.1 (COMSOL, Inc., Burlington, MA) (Fig. 1g–h). The boundary conditions were set to be 4.5 kV at the paper tip and 0 V at the MS inlet, corresponding to the operating condition in the experiments. The potential distribution for angle 60° is shown in Fig. 1g. A zoom-in view of the electric field for angle 30° is shown in the inset of Fig. 1h. The highest electric field strength was found to be at the of the paper tips, which supports the observation that spray only occurs at the sharp corners of the paper substrates (Fig. 1a). The field strength at the tip of the paper spray is plotted as a function of the angle in Fig. 1h. As expected, electric field density is higher at the tips of paper cut to smaller angles, which is favorable for generating the spray (Fig. 1c).

Sample load is another important factor that affects paper spray ionization. Solutions of 1 μg/mL imatinib and 1 μg/mL imatinib-d8, pre-mixed in bovine whole blood, were used to explore the relationship between sample load and paper substrate size for quantitative analysis. Three homologous paper triangle substrates (T1, T2, T3) of different areas were prepared: they were 7.5 mm × 8 mm for T1 paper substrates, 11.9 mm × 12.7 mm for T2 paper substrates, and 16.8 mm × 17.9 mm for T3 paper substrates so that the area ratio of T1, T2 and T3 was 1:2.5:5. The spray solvent volumes applied to substrates T1, T2, and T3 were 10, 25, 50 μL MeOH:water (1:1), which is proportional to their areas. For each size of paper substrate, three different blood sample amounts (0.5, 1.25, 2.5 μL) were preloaded in the middle of the substrate which were then dried and tested. Two key characteristics, MS sig-

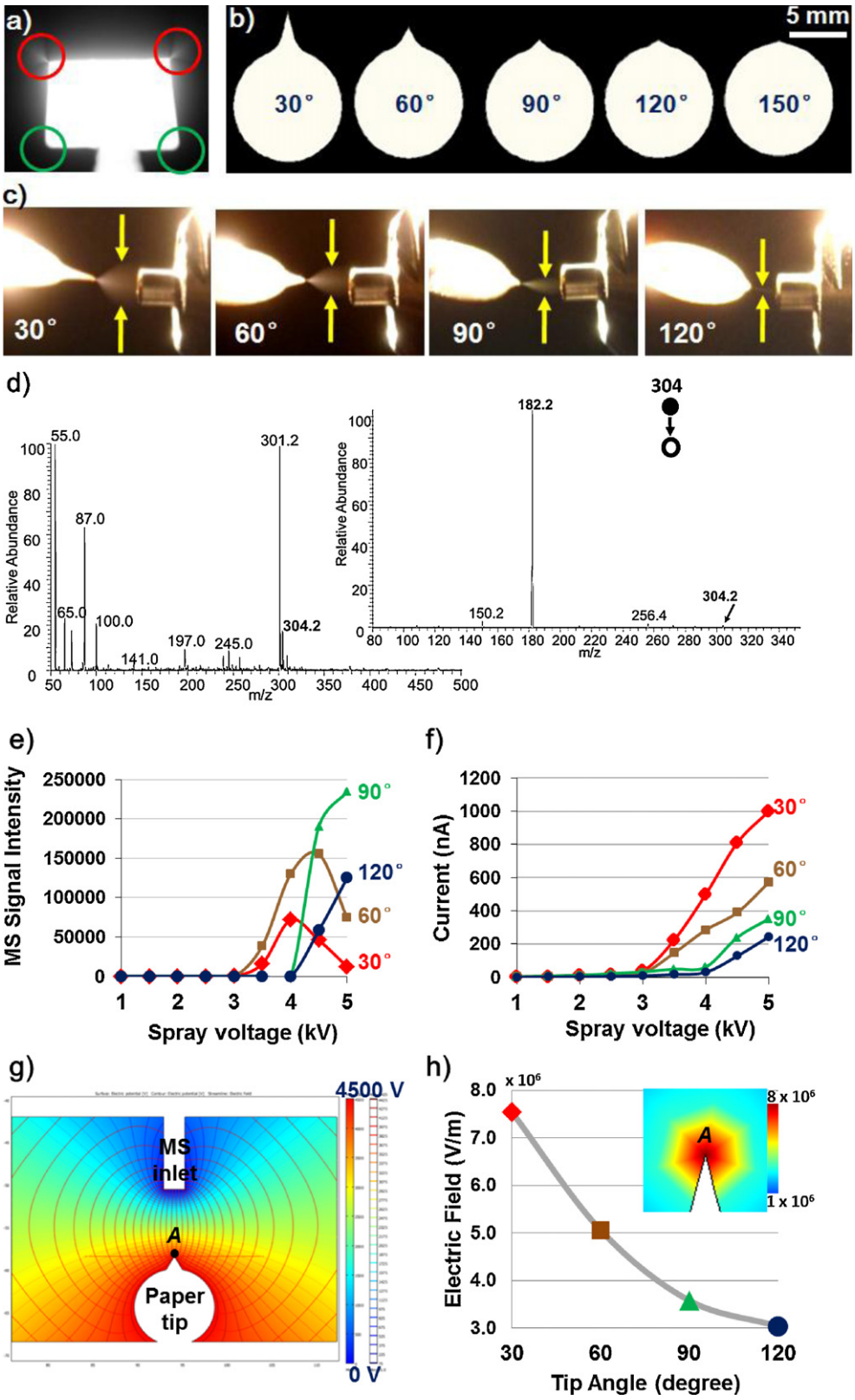

Fig. 1. (a) Spray plumes on a rectangular paper substrate. (b) Paper substrates with different tip angles of 30°, 60°, 90°, 120° or 150°. (c) Spray plumes recorded for paper substrates with tip angles of 30°, 60°, 90° and 120°. (d) MS and MS/MS spectra of 1 μg/mL cocaine in MeOH:water (1:1) as spray solvent, paper substrate with a tip angle 90°, spray voltage 4.5 kV. (e) Peak intensity of cocaine fragment ion *m*/*z* 182 and (f) total spray current as a function of the spray voltage. (g) Simulated potential distribution simulation (tip angle = 60°). (h) Electric field strength at the paper substrate tip as a function of tip angle. Inset: zoomed-in view of electric field distribution at a paper substrate tip (tip angle = 30°).

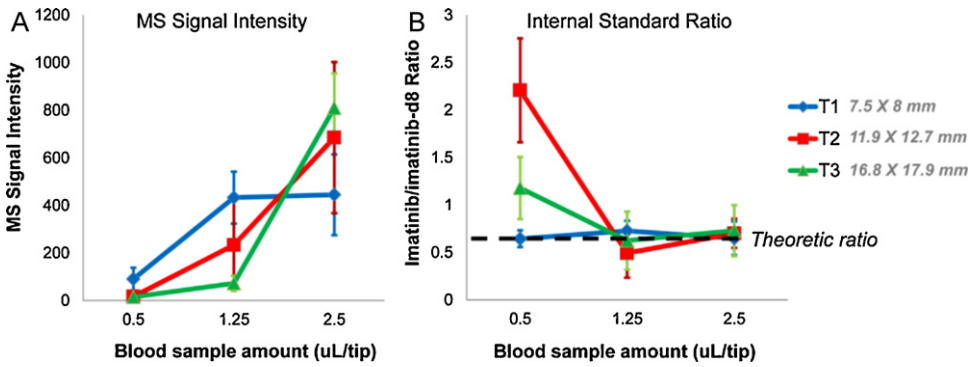

Fig. 2. Peak intensity of imatinib fragment ion *m/z* 394 (a) and imatinib/imatinib-d8 ratio (b) as a function of sample load for different paper sizes (T1: 5 mm × 8 mm; T2: 11.9 mm × 12.7 mm; and T3: 16.8 mm × 17.9 mm). 1 μg/mL imatinib and imatinib-d8 in whole bovine blood.

nal intensity and the ratio between the signal for the drug (imatinib) and its internal standard (imatinib-d8), were investigated.

The peak intensity of the imatinib fragment ion *m/z* 394 generally increased as the blood sample amount increased for each paper substrate size (Fig. 2a). However, 1.25 μL and 2.5 μL samples loaded onto the T1 substrate gave similar MS signal intensities. The T2 and T3 substrate behaved unexceptionally. It is concluded that the T1 substrate had already reached its maximum extraction limit (its saturation sample load) for volumes between 1.25 and 2.5 μL. Since the MS signal intensity of the T2 and T3 paper substrates was still rising at 2.5 μL sample load, the T2 and T3 substrates should have unique saturation sample loads that are higher than that for the T1. For 1.25 μL sample load, the signal intensity dropped as the size of paper substrate increased due to the larger volume of spray solvent, which helped to dilute the blood sample and lowered the signal of the analyte, whereas for the 2.5 μL sample load, the trend was opposite in that the highest signal intensity appeared using the T3 paper substrate. Moreover, for the same sample-to-solvent ratio of 0.5 (0.5 μL blood on T1, 1.25 μL blood on T2 and 2.5 μL blood on T3), the larger paper tips yielded much improved signal intensities.

To eliminate various sources of error in quantitation, the ratio between the drug and its internal standard, instead of the absolute signal intensity of the drug, was used to determine the concentration of the drug in blood. In Fig. 2b, the dashed line represents the theoretical ratio between the drug and its internal standard. Most of the ratios measured were found to be in agreement with the theoretical values except for the 0.5 μL blood on the T2 and T3 paper substrates. This deviation from the theoretical ratio appears to be because 0.5 μL blood was too little to provide accurate quantitative results using the larger T2 and T3 paper substrates. This indicates that each substrate size also has a minimum sample load requirement for quantitative analysis.

The process of analyte dissolution and distribution with the spray solution on the paper was also studied. Consideration was given to three processes by which the analytes might be transferred during paper spray: (1) capillary action/wetting, (2) electrophoresis and (3) bulk solution movement as a surface liquid film. An equilateral triangle paper substrate with length along each side of 3 cm and three analytes (caffeine, imatinib and bradykinin 2–9) were used for the study (Fig. 3). The three corners of the large paper triangle were cut after the paper had dried for each test, and the peak intensities of fragment ions (*m/z* 138 for caffeine, *m/z* 394 for imatinib, and *m/z* 404 for bradykinin 2–9) were recorded for each corner of each triangle (Fig. 4a).

Transport by capillary action was examined by applying 100 μL of solvent slowly to the middle of the paper to wet the whole paper. Under these conditions, analytes moved through the paper only by capillary action. As shown in the upper panel of Fig. 4b, similar signal intensities were obtained for all three compounds

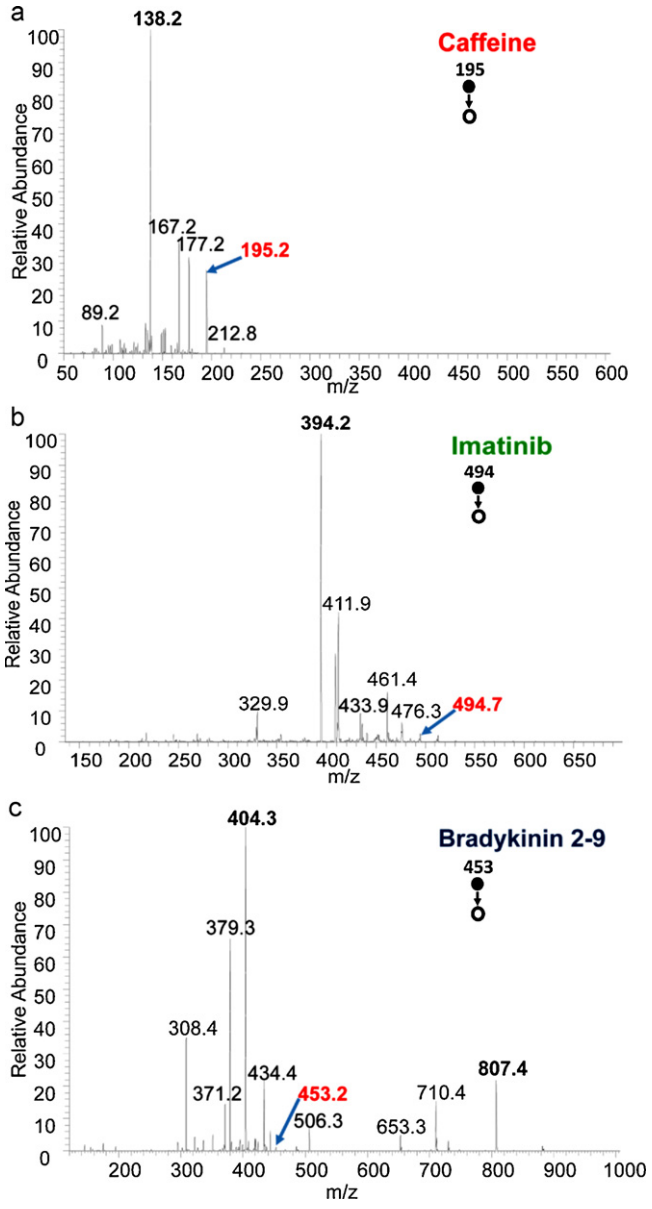

Fig. 3. MS/MS spectra of caffeine, imatinib and bradykinin 2–9 using paper spray ionization.

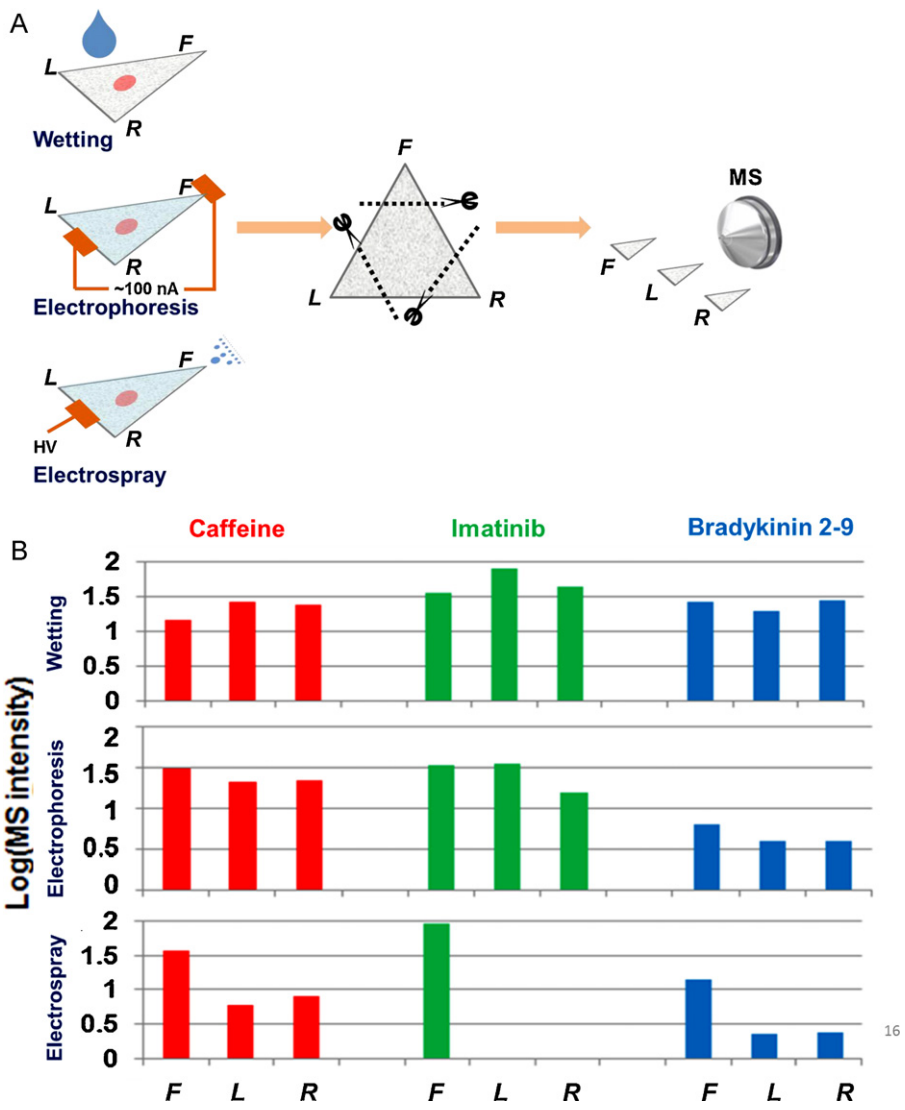

Fig. 4. (a) Schematic illustration of the experimental design for studying the analyte dissolution and transfer on paper (F: front; L: left; R: right). (b) Distributions of caffeine (red), imatinib (green) and bradykinin 2–9 (blue) on paper under different conditions. Peak intensities for the transitions m/z 195 → 138 for caffeine, m/z 494 → 394 for imatinib and m/z 453 → 404 for bradykinin 2–9 were monitored. (For interpretation of the references to color in text, the reader is referred to the web version of the article.)

(caffeine, imatinib and bradykinin) at all three corners, which suggests that the analytes were evenly distributed by capillary action. To examine the contribution of electrophoretic flow, electrodes were attached to the base and the apex of the large paper triangle and a DC electric current of 100 nA was established between these electrodes during the same wetting process as described above. The electric current was equivalent to that under normal paper spray condition. An even distribution was observed again, as shown in the middle panel in Fig. 4b, and this result indicates that electrophoretic transfer does not play a significant role. Lastly, normal paper spray was implemented, so that capillary and electrophoretic effects operated in addition to bulk solution movement due to the driving force of the spray leaving the tip. Since a relatively large amount of solvent was added to wet the paper, excess solvent formed a liquid film on the paper surface. As the spray occurred at the tip of the paper, the solvent was consumed and the liquid on the paper was pulled toward the spraying tip. As shown in the bottom panel in Fig. 4b, higher signal intensities were observed at the spraying tip for all three analytes. This demonstrates the significant role of bulk solvent movement in transferring analyte.

With the knowledge gained from the studies described above, a paper spray cartridge was designed and fabricated using SLA (stereo lithography apparatus) [45]. SLA resin Nanoform 15120 (DSM Somos) was chosen as the cartridge material as it has a high glass-transition temperature and is relatively chemically inert, especially to organic solvents [46]. The cartridge consisted of three main parts: holder, lid and electrode (Fig. 5a). A paper substrate was sandwiched between the holder and the lid, with its sharp tip extending through the front opening to allow unimpeded spray. The lip structure was used to protect the paper tip from damage during the handling of the cartridge. The lid could be opened easily or locked onto the holder through the side clips, which allowed the paper inside could be replaced as necessary. Through the hole in the lid, sample and solvent could be applied to the paper substrate. A bolt through a nut embedded in the cartridge was in contact with the paper to allow application of the high voltage.

The paper substrate was cut into a polygon (Fig. 5b) with the spray tip having the sharpest angle of less than 90°, which suppressed spray from the other corners. Since bulk solvent movement is critical for signal intensity, five props (three on the bottom and two on the lid) were fabricated to support the large paper tip (Fig. 5c). This design prevents paper bending due to wetting by the large amount of solvent. The configuration of interlaced props with curved surfaces minimized the contact area between the resin and

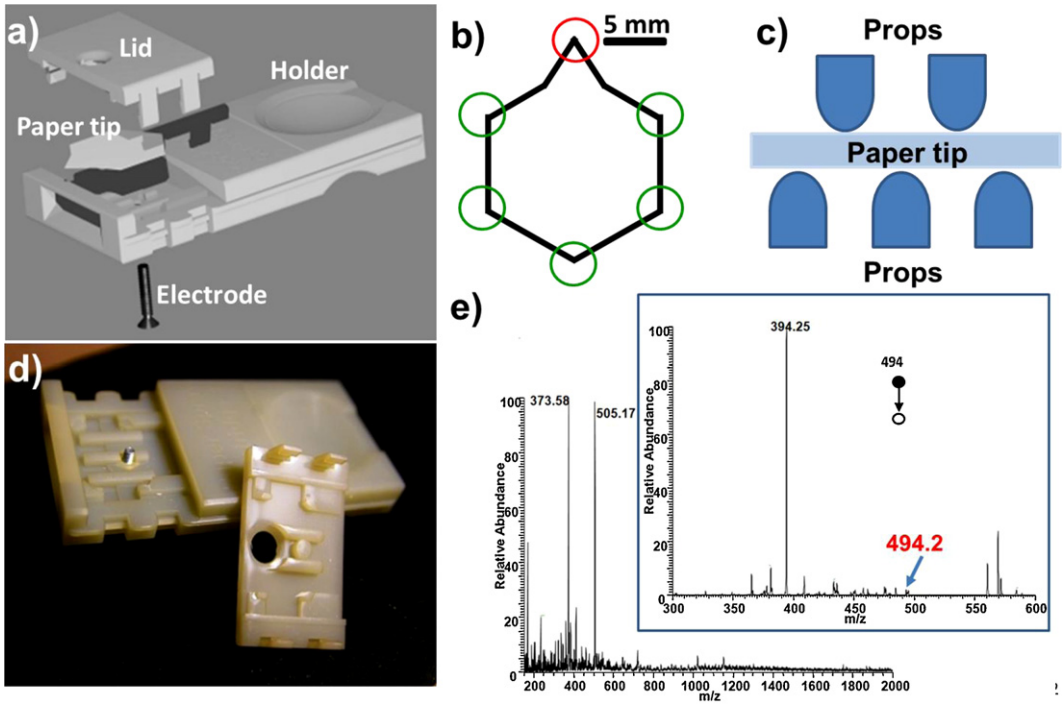

Fig. 5. (a) Paper spray cartridge design. (b) Design of the paper substrate (red: spray point). (c) Support of the paper substrate with props inside cartridge. (d) Cartridge fabricated using SLA. (e) MS and MS/MS spectra of 1 μg/mL imatinib in whole bovine blood using paper spray cartridge with MeOH:water (1:1) as spray solvent, spray voltage 4.5 kV. (For interpretation of the references to color in text, the reader is referred to the web version of the article.)

the paper, and less solvent accumulated due to physical contact. A photo of the whole cartridge is shown in Fig. 5d. The imatinib in blood at 1 μg/mL was easily detected using this cartridge and the MS and MS/MS spectra are shown in Fig. 5e.

The use of paper spray for clinical analysis potentially can be implemented with this type of simple cartridge. The cost of both cartridge and paper is low enough that the cartridge could serve as a disposable item in practice and be used for analysis without any concern regarding cross-contamination. The sample preparation process is simple and unskilled operators are able to use the cartridge for analysis. The entire test is fast and the results become available 1 min after putting the raw sample onto the cartridge. All these advantages have the potential to contribute to the development of personalized medicine using paper spray mass spectrometry.

4. Conclusions

Paper spray ionization has been developed for direct MS analysis of complex mixtures with minimum sample treatment. The effects of experimental variables have been delineated and capabilities for analysis of clinical samples have been verified. Paper spray cartridges have been built as sample media for utilization of paper spray MS analysis for point-of-care diagnosis and other clinical applications.

Acknowledgements

This work was supported by the National Science Foundation (CHE 0847205 and CHE 0848650), National Science Foundation Instrumentation Development for Biological Research (DBI 0852740), National Institutes of Health (1R21RR031246-01 and 1R21EB009459-01) and the Alfred Mann Institute at Purdue.

References

[1] M. Yamashita, J.B. Fenn, Electrospray ion-source—another variation on the free-jet theme, Journal of Physical Chemistry 88 (1984) 4451–4459.
[2] T.R. Covey, E.D. Lee, J.D. Henion, High-speed liquid chromatography/tandem mass spectrometry for the determination of drugs in biological samples, Analytical Chemistry 58 (1986) 2453–2460.
[3] B.A. Thomson, Atmospheric pressure ionization and liquid chromatography mass spectrometry—together at last, Journal of the American Society for Mass Spectrometry 9 (1998) 187–193.
[4] F. Saint-Marcoux, F.L. Sauvagge, P. Marquet, Current role of LC–MS in therapeutic drug monitoring, Analytical and Bioanalytical Chemistry 388 (2007) 1327–1349.
[5] P.J. Taylor, C.-H. Tai, M.E. Franklin, P.I. Pillans, The current role of liquid chromatography–tandem mass spectrometry in therapeutic drug monitoring of immunosuppressant and antiretroviral drugs, Clinical Biochemistry 44 (2011) 14–20.
[6] A. Schulze, M. Lindner, D. Kohlmuller, K. Olgemoller, E. Mayatepek, G.F. Hoffmann, Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications, Pediatrics 111 (2003) 1399–1406.
[7] B. Wilcken, V. Wiley, J. Hammond, K. Carpenter, Screening newborns for inborn errors of metabolism by tandem mass spectrometry, New England Journal of Medicine 348 (2003) 2304–2312.
[8] H.H. Maurer, Liquid chromatography–mass spectrometry in forensic and clinical toxicology, Journal of Chromatography B: Biomedical Sciences and Applications 713 (1998) 3–25.
[9] C.E. Parker, T.W. Pearson, N.L. Anderson, C.H. Borchers, Mass-spectrometry-based clinical proteomics—a review and prospective, Analyst 135 (2010) 1830–1838.
[10] N.L. Anderson, N.G. Anderson, The human plasma proteome—history, character, and diagnostic prospects, Molecular and Cellular Proteomics 1 (2002) 845–867.
[11] B. Shushan, A review of clinical diagnostic applications of liquid chromatography–tandem mass spectrometry, Mass Spectrometry Reviews 29 (2010) 930–944.
[12] R.G. Cooks, Z. Ouyang, Z. Takats, J.M. Wiseman, Detection technologies. Ambient mass spectrometry, Science 311 (2006) 1566–1570.
[13] Z. Takats, J.M. Wiseman, B. Gologan, R.G. Cooks, Mass spectrometry sampling under ambient conditions with desorption electrospray ionization, Science 306 (2004) 471–473.
[14] R.B. Cody, J.A. Laramee, H.D. Durst, Versatile new ion source for the analysis of materials in open air under ambient conditions, Analytical Chemistry 77 (2005) 2297–2302.

[15] H.W. Chen, G. Gamez, R. Zenobi, What can we learn from ambient ionization techniques? Journal of the American Society for Mass Spectrometry 20 (2009) 1947–1963.
[16] G.J. Van Berkel, S.P. Pasilis, O. Ovchinnikova, Established and emerging atmospheric pressure surface sampling/ionization techniques for mass spectrometry, Journal of Mass Spectrometry 43 (2008) 1161–1180.
[17] A. Venter, M. Nefliu, R.G. Cooks, Ambient desorption ionization mass spectrometry, Trac-Trends in Analytical Chemistry 27 (2008) 284–290.
[18] Z. Takáts, J.M. Wiseman, R.G. Cooks, Ambient mass spectrometry using desorption electrospray ionization (DESI): instrumentation, mechanisms and applications in forensics, chemistry, and biology, Journal of Mass Spectrometry 40 (2005) 1261–1275.
[19] J.M. Wiseman, D.R. Ifa, Y. Zhu, C.B. Kissinger, N.E. Manicke, P.T. Kissinger, R.G. Cooks, Desorption electrospray ionization mass spectrometry: imaging drugs and metabolites in tissues, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 18120–18125.
[20] D.J. Weston, R. Bateman, I.D. Wilson, T.R. Wood, C.S. Creaser, Direct analysis of pharmaceutical drug formulations using ion mobility spectrometry/quadrupole-time-of-flight mass spectrometry combined with desorption electrospray ionization, Analytical Chemistry 77 (2005) 7572–7580.
[21] G. Hopfgartner, E. Bourgogne, Quantitative high-throughput analysis of drugs in biological materices by mass spectrometry, Mass Spectrometry Reviews 22 (2003) 195–214.
[22] J.P. Williams, J.H. Scrivens, Rapid accurate mass desorption electrospray ionisation tandem mass spectrometry of pharmaceutical samples, Rapid Communications in Mass Spectrometry 19 (2005) 3643–3650.
[23] J.P. Williams, R. Lock, V.J. Patel, J.H. Scrivens, Polarity switching accurate mass measurement of pharmaceutical samples using desorption electrospray ionization and a dual ion source interfaced to an orthogonal acceleration time-of-flight mass spectrometer, Analytical Chemistry 78 (2006) 7440–7445.
[24] C.N. McEwen, R.G. McKay, B.S. Larsen, Analysis of solids, liquids, and biological tissues using solids probe introduction at atmospheric pressure on commercial LC/MS instruments, Analytical Chemistry 77 (2005) 7826–7831.
[25] G. Huang, H. Chen, X. Zhang, R.G. Cooks, Z. Ouyang, Rapid screening of anabolic steroids in urine by reactive desorption electrospray ionization, Analytical Chemistry 79 (2007) 8327–8332.
[26] J.D. Harper, N.A. Charipar, C.C. Mulligan, X. Zhang, R.G. Cooks, Z. Ouyang, Low-temperature plasma probe for ambient desorption ionization, Analytical Chemistry 80 (2008) 9097–9104.
[27] D.R. Ifa, A.U. Jackson, G. Paglia, R.G. Cooks, Forensic applications of ambient ionization mass spectrometry, Analytical and Bioanalytical Chemistry 394 (2009) 1995–2008.
[28] N. Talaty, C.C. Mulligan, D.R. Justes, A.U. Jackson, R.J. Noll, R.G. Cooks, Fabric analysis by ambient mass spectrometry for explosives and drugs, Analyst 133 (2008) 1532–1540.
[29] H. Chen, A. Venter, R.G. Cooks, Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation, Chemical Communications (2006) 2042–2044.
[30] D.R. Justes, N. Talaty, I. Cotte-Rodriguez, R.G. Cooks, Detection of explosives on skin using ambient ionization mass spectrometry, Chemical Communications (2007) 2142–2144.
[31] R.B. Cody, J.A. Laramée, H.D. Durst, Versatile new ion source for the analysis of materials in open air under ambient conditions, Analytical Chemistry 77 (2005) 2297–2302.
[32] Z. Takáts, J.M. Wiseman, B. Gologan, R.G. Cooks, Mass spectrometry sampling under ambient conditions with desorption electrospray ionization, Science 306 (2004) 471–473.
[33] P. Nemes, A. Vertes, Laser ablation electrospray ionization for atmospheric pressure, in vivo, and imaging mass spectrometry, Analytical Chemistry 79 (2007) 8098–8106.
[34] J.S. Sampson, A.M. Hawkridge, D.C. Muddiman, Construction of a versatile high precision ambient ionization source for direct analysis and imaging, Journal of the American Society for Mass Spectrometry 19 (2008) 1527–1534.
[35] J.S. Sampson, A.M. Hawkridge, D.C. Muddiman, Development and characterization of an ionization technique for analysis of biological macromolecules: liquid matrix-assisted laser desorption electrospray ionization, Analytical Chemistry 80 (2008) 6773–6778.
[36] J. Shiea, M.-Z. Huang, H.-J. HSu, C.-Y. Lee, C.-H. Yuan, I. Beech, J. Sunner, Electrospray-assisted laser desorption/ionization mass spectrometry for direct ambient analysis of solids, Rapid Communications in Mass Spectrometry 19 (2005) 3701–3704.
[37] H. Wang, J.J. Liu, R.G. Cooks, Z. Ouyang, Paper spray for direct analysis of complex mixtures using mass spectrometry, Angewandte Chemie-International Edition 49 (2010) 877–880.
[38] J.J. Liu, H. Wang, N.E. Manicke, J.M. Lin, R.G. Cooks, Z. Ouyang, Development, characterization, and application of paper spray ionization, Analytical Chemistry 82 (2010) 2463–2471.
[39] R.G. Cooks, N.E. Manicke, A.L. Dill, D.R. Ifa, L.S. Eberlin, A.B. Costa, H. Wang, G. Huang, Z. Ouyang, New ionization methods and miniature mass spectrometers for biomedicine: DESI imaging for cancer diagnostics and paper spray ionization for therapeutic drug monitoring, Faraday Discussions 149 (2011) 247–267.
[40] N.E. Manicke, Q. Yang, H. Wang, S. Oradu, Z. Ouyang, R.G. Cooks, Assessment of paper spray ionization for quantitation of pharmaceuticals in blood spots, International Journal of Mass Spectrometry 300 (2011) 123–129.
[41] H. Wang, N.E. Manicke, Q. Yang, L. Zheng, R. Shi, R.G. Cooks, Z. Ouyang, Direct analysis of biological tissue by paper spray mass spectrometry, Analytical Chemistry 83 (2011) 1197–1201.
[42] C.H. Arnaud, Technology renews a basic approach, Chemical & Engineering News 89 (2011) 13–17.
[43] J.M. Wiseman, C.A. Evans, C.L. Bowen, J.H. Kennedy, Direct analysis of dried blood spots utilizing desorption electrospray ionization (DESI) mass spectrometry, Analyst 135 (2010) 720–725.
[44] V. Kertesz, G.J. Van Berkel, Fully automated liquid extraction-based surface sampling and ionization using a chip-based robotic nanoelectrospray platform, Journal of Mass Spectrometry 45 (2010) 252–260.
[45] M. Yu, M. Fico, S. Kothari, Z. Ouyang, W.J. Chappell, Polymer-based ion trap chemical sensor, IEEE Journal of Sensors 6 (2006) 1429–1434.
[46] J.D. Maas, P.I. Hendricks, O. Zheng, R.G. Cooks, W.J. Chappell, Miniature monolithic rectilinear ion trap arrays by stereolithography on printed circuit board, IEEE Journal of Microelectromechanical Systems 19 (2010) 951–960.