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Microfluidic paper-based analytical device for colorimetric screening prior to mass spectrometry analysis

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Abstract: In order to improve the efficiency of mass spectrometry(MS) instrument, a microfluidic paper-based analytical device (μPAD) was designed for sample loading and pre-screening. Samples loaded on μPAD can be split into two separated detection zones. Colorimetric detection with the naked eye can be viewed as fast screening. Samples with significantly lower or higher colorimetric response than threshold may be ignored. For suspicious samples, final detection with much higher sensitivity would be carried out with MS. Using the present method, quantifications of Ang II in raw serum with both colorimetry and MS were achieved. For colorimetric detection, the resulting linear range of 200～1 000 μmol/L was established, and the visual detection limit was in the range of 150～200 μmol/L. For MS detection, the linear dynamic range for Ang II was 5～500 μmol/L. The limit of detection (LOD) was measured to be 1.9 μmol/L using bradykinin as the internal standard. The result indicates that this protocol would enable easy sample transportation, rapid screening and sensitive MS measurement with a single μPAD device.

Key words: paper-based analytical device; paper spray ionization; fast screening; colorimetric analysis

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纸芯片用于比色法筛查和质谱鉴定的研究

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摘要:设计了一种用于负载和初筛样品的纸芯片:利用纸采集液体样品,并将其分别引入预设的比色区域和质谱分析区域.利用比色法快速筛查出样品,排除浓度明显过高的样品,只需将剩余样品带回实验室,进行质谱定性定量分析,从而提高仪器使用效率.将其应用于复杂基质中多肽的分析,比色法可筛掉浓度过高的血管紧张素 II(线性范围为 200～1 000 μmol/L,检出限范围为 150～200 μmol/L),然后用质谱法进行最终鉴

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定(线性范围为5～500 μmol/L,检出限为1.9 μmol/L).配合不同比色体系,此方法可望实现质谱鉴定前的样品采集以及快速筛查.

关键词:纸芯片;纸喷雾质谱;快速筛查;比色分析

0 Introduction

Mass spectrometry (MS) is well-known for its sensitivity and selectivity, and it is capable of rapid sampleidentification and quantification[1-4]. However, bench top MS instrument is usually not suitable for field applications and at-home diagnosis due to its weight, size and power consumption. With the development of portable miniature MS[5-8], its field application and at-home diagnosis have been achieved, but the analytical performance may be greatly sacrificed[9]. Thus, the strategy of bringing raw samples to laboratory is still receiving much attention.

Presently, some fast sample analysis techniques, including desorption electrospray ionization (DESI)[10-12], together with more than 20 kinds of ambient ionization methods, such as direct analysis in real time (DART)[13-14], extractive electrospray ionization (EESI)[15-17] and liquid microjunction surface sampling probing (LMJ-SSP)[18], have been reported for direct detection of raw samples without chromatographic separation. With a proper sampling technique, such as swabbing and direct deposition, paper can serve as an easy substrate for the transfer process of raw samples. Then, paper spray (PS) can be a facile ambient ionization technique for collected raw samples[19-21]. However, if all collected raw samples needed to be taken to the lab for MS analysis, the efficiency of the instrument would be sacrificed, especially in case that excessive samples are daily dealt with, for example, in environmental quality monitoring or in some situations requiring an emergency response[22]. Thus, if an additional screening process could be introduced between sample collection using filter paper and final PS MS analysis, samples with significantly higher or lower concentrations than threshold would be ignored, which would greatly increase instrument efficiency and decrease sample numbers transferred to the lab.

A screening process which can distribute the same sample into different detection zones and facilitate both fast screening process on paper and MS detection for suspicious samples is needed, which just can be realized with the recently developed microfluidic paper-based analytical devices (μPADs)[23-30]. Three-dimensional μPADs recently reported[31-33,34-36] mainly carry the advantages of small size, disposability, portability, easy use and different detection zones. Colorimetry[37-39] is the most widely used detection method for μPADs, where specific chromogenic reagents are applied to the device and the developed color intensity and/or hue correlates with the concentration of the analyte[40-42]. The analysis results can be visualized with the naked eye, without additional analytical equipments, which is adequate for diagnosis that only requires a yes/no answer or a semi-quantitative detection.

Thus, we aimed to combine μPAD with PS MS in order to develop a method that can screen samples prior to MS analysis. Although a microfluidic chip coupled with MS has been intensively studied, there have been few cases for off-line hyphenation of the microfluidic chip coupled with PS MS[43]. As for on-line hyphenation of μPAD and PS MS, no relative study has been reported. This method might be useful to increase instrument efficiency in case either excessive samples are dealt with daily (such as in field analysis), or at-home diagnosis is carried out to reduce medical expenses in extremely poor areas by transferring only suspicious blood or urine samples for lab testing.

Based on this principle, the protocol of μPAD-

PS MS has been designed in this study. This technique comprises three steps: ① splitting the sample into two separate detection zones via μPAD; ② rapid screening by colorimetric detection with the naked eye; ③ sensitive measurement by PS MS. With the present method, the analysis of peptides, including Ang II, bradykinin and KCTCCA in pure solvent was tested qualitatively. Besides, combination of colorimetric and MS detection for Ang II in complex matrices (rabbit whole blood, raw serum, cell culture medium (CCM) and raw urine) were tested without any pretreatment. Quantifications with both colorimetric and MS detection in raw serum were also achieved.

1 Experimental

1.1 Materials and reagents

HPLC grade methanol (CH_3OH), methyl violet and tetrabromophenol blue were purchased from Honeywell Burdick & Jackson Inc. (USA). Hydrochloric acid, sodium hydroxide and Sodium citrate were obtained from Sinopharm Chemical Reagent Co. Ltd. (Beijing, China). Acetic acid, angiotensin II (Ang II), bradykinin, KCTCCA, rabbit whole blood and raw serum (bovine) were purchased from Sangon Biological Engineering Technology & Services Co. Ltd. (Shanghai, China). Human urine samples were donated by healthy volunteers. All these reagents were used directly without any further purification. Distilled water (18.2 MΩ) was produced by Milli-Q system (Millipore Inc., Bedford, MA, USA). 3MM Chromatograph paper was purchased from Whatman International Ltd. (Maidstone, England).

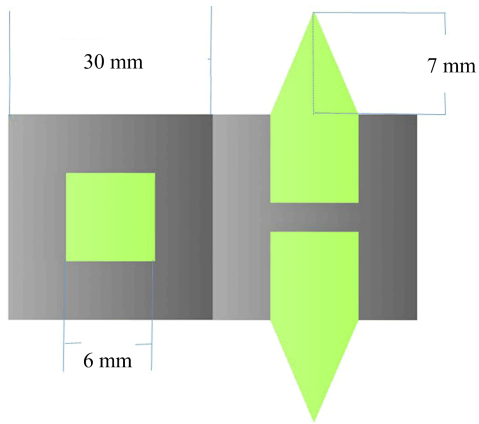
CCM consisted of DMEM (dulbecco's modified eagle medium)/High Glucose (89%), serum (10%) and penicillin-streptomycin (1%) was stored at 4 ℃. Rabbit whole blood, raw serum and raw urine were stored at −20 ℃. Peptide was spiked into raw urine, rabbit whole blood, raw serum or CCM with various dilution ratios (>1∶10).

During the colorimetric detection, 250 mmol/L citrate buffer solution (pH 1.8) was prepared in CH_3CH_2OH/H_2O (volume ratio 8∶92); 9 mmol/L tetrabromophenol blue was prepared in CH_3CH_2OH/H_2O (volume ratio 95∶5). All the solutions of the analytes were prepared in H_2O unless otherwise noted.

All the solutions of the analytes were prepared in CH_3OH/H_2O (volume ratio 3∶1) with the addition of 0.5% acetic acid to increase ionization efficiency unless otherwise noted.

1.2 Design and fabrication of the μPAD

Detailed design of the μPAD is shown in Fig. 1. The hydrophilic area consisted of one sample loading zone (6 mm×6 mm on the first layer), two reservoir zones (6 mm×6 mm on the secondary layer) and two detection zones (6 mm×7 mm on the secondary layer). Two detection zones were cut into triangular shape as the colorimetric and MS detection zones. Firstly, we drew the design on the chromatography paper by a pencil. Secondly, we cut the device along the marked design with a craft cutter. Thirdly, we hand-waxed the hydrophobic area of the paper with a crayon. Finally the wax pattern was melted in an oven (120 ℃ for about 3 min) to define the hydrophobic barriers and hydrophilic channels, and the pencil marks were then erased with a rubber.



Size is included. The hydrophilic area consists of one sample loading zone, two reservoir zones and two detection zones. Two detection zones are cut into triangular shape to make the colorimetric and MS detection zones parallel.

Fig. 1　The design of μPAD

In addition, a much simpler paper-based device can be obtained through hand drawing, hand cutting, hand waxing and heating with ironing. Then with the aid of a small reagent kit, anyone can play this paper-based device at home at extremely low cost.

1.3 Colorimetric detection of peptide

The previously reported method for peptide and protein detection on μPADs was used here[44]. 0.5 μL priming solution (volume ratio of ethanol/water was 8∶92, buffered with sodium citrate (250 mmol/L, pH 1.8)) was spotted on the triangle of the μPADs and dried for 10 min at room temperature. Then, 0.5 μL reagent solution (9 mmol/L tetra bromophenol blue in ethanol/ water with volume ratio 95∶5) was spotted on the top of the priming solution and dried for 10 min at room temperature. Analyte solution (2～10 μL) was then added onto the top layer of the μPADs. Lastly CH_3OH/H_2O (volume ratio 3∶1, 10 μL) was added on the sampling zone three times for elution.

1.4 Mass spectrometry and paper-based ESI spray

All experiments were performed using a Thermo Fisher Scientific LTQ Velos Pro mass spectrometer (San Jose, CA, USA). The temperature of the MS capillary inlet was set as 275 ℃. The voltage used for paper spray ionization was 4.5 kV in positive mode. To perform collision-induced dissociation (CID), ions of interest were isolated using an m/z window width of 1 unit. Helium was used as the collision gas, and the CID energy was set at 35% with a duration time of 30 ms for tandem mass spectrometry. All mass spectra were processed with Xcalibur® software.

Conductive copper for applying high voltage was stuck to the bottom layer for HV electrical contact. The device was placed before the mass spectrometer at a distance of 5 mm. The top layer of the device was a preloaded analyte solution (10 μL) and CH_3OH/H_2O (volume ratio 3∶1) was added to elute the sample. Then 4.5 kV was applied to generate spray. Lastly, spray droplets containing the sample were transferred into the atmospheric interface of the mass spectrometry. Tandem mass spectrometry was applied to confirm the analyte as well as in complex matrices.

During the entire experiment, insulation for operators from the DC HV should be mandatory.

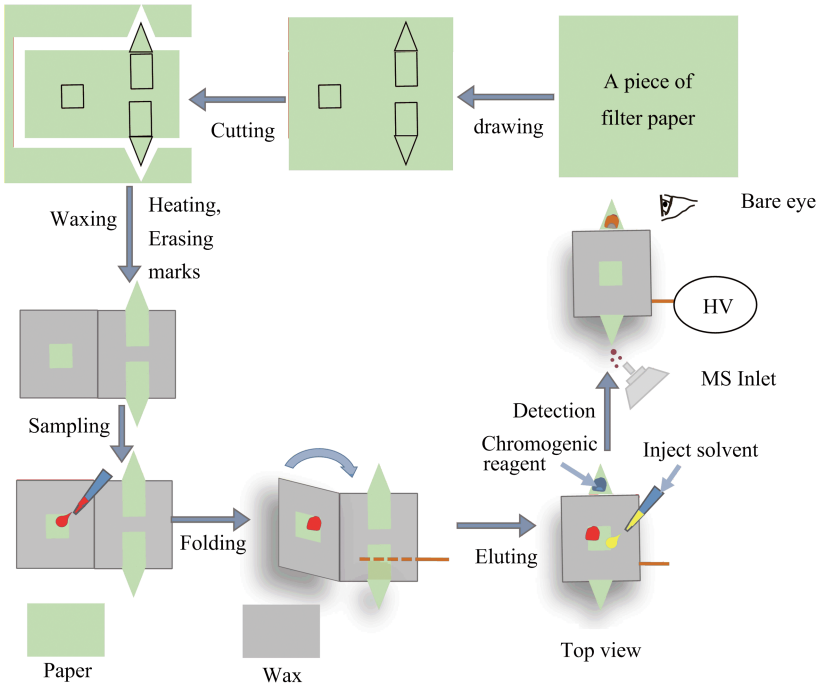
2 Results and discussion

2.1 Device design

The protocol of μPAD-PS MS in this study and photographs of the unfolded μPAD are shown in Fig. 2. The analyte solution (2～10 μL) was added onto the top layer of the μPAD and it was dried for about 30 min . Then the device was folded for contact with the first and second layers of the μPAD and around 10 μL of supply solution was then added for eluting the analyte to the two detection zones. In a word, our method combined colorimetric detection with on-line MS detection via a μPAD. In at-home diagnosis, when combined with some specific chromogenic reagents, patients can conduct preliminary diagnosis at home with a diagnostic kit including pre-made paper-based device and ready-to-use chemical solutions. Then, only the suspicious samples need be transferred to lab for further identification without additional requirement, such as cooling box for sample transfer. This would be especially useful in extremely poor areas to reduce medical expenses by carrying out expensive lab test for suspicious samples only.

2.2 Dye migration and MS detection

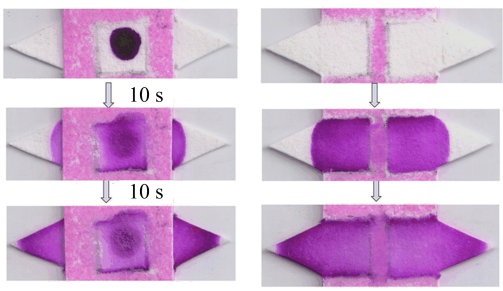
To prove that the small molecules added to the top layer of the μPADs can be split to two detection zones, we used methyl violet with a visible violet color to visualize the sample migration on μPADs. On-device images of methyl violet migration and associated MS detection are shown in Fig. 3. Fig. 3(a) shows the result of dye migration in which methyl violet solution (1 000 μg·mL^{-1}, 2 μL) was added to the sample loading zone. CH_3OH (10 μL) was used to elute the sample to the detection zones three times. The



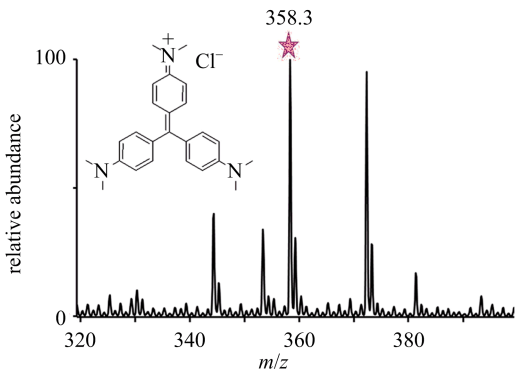
Firstly, the design is drawn on the paper by a pencil. Secondly, the device is cut along the marked design with a craft cutter. Thirdly, the hydrophobic area of the paper is hand-waxed with a crayon. Finally the wax pattern is melted in an oven. Chromogenic reagents are added for colorimetric screening. High voltage is added for MS detection.
(a) A piece of paper can be used for colorimetric screening and MS detection by simple steps

One dollar is used as reference.
(b) Photographs of the unfolded μPAD

Fig. 2　The designed paper-based device



The whole time needed for dye migration is 20 s.
(a) The photo of the top and bottom view of dye migration



(b) Full mass spectrum of methyl violet (1 000 μg·mL^{-1}, 2 μL) with MeOH/H_2O (volume ratio 3:1) as spray solvent.

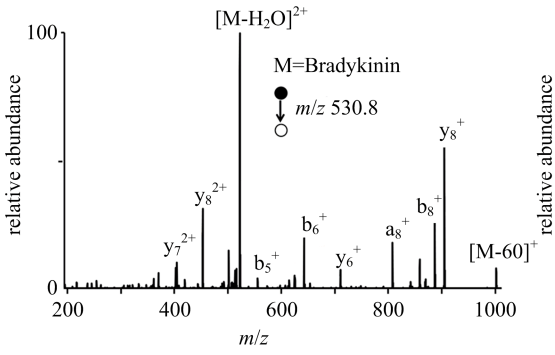
Fig. 3　Dye migration and MS detection

whole elution time was about 20 s. During this process, we could see that the violet migrated from the first layer to the second layer to the detection zones. The result shows that small molecules such as methyl violet can be split into the two detection zones. The methyl violet that migrated to the

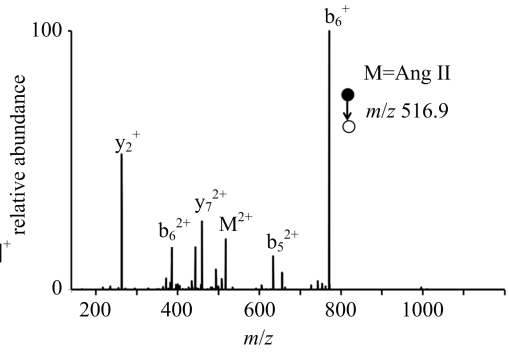
detection zones was then subjected to the conventional PS MS experiment, with CH_3OH/H_2O (volume ratio 3∶1) used as the elution solution and PS solvent. Fig. 3(b) shows the result of MS detection of methyl violet (m/z 358.3) solution. In full MS, we could see the molecular ion peak of methyl violet (m/z 358.3). Its tandem MS spectra confirmed the presence of methyl violet.

2.3 Peptides migration and MS detection

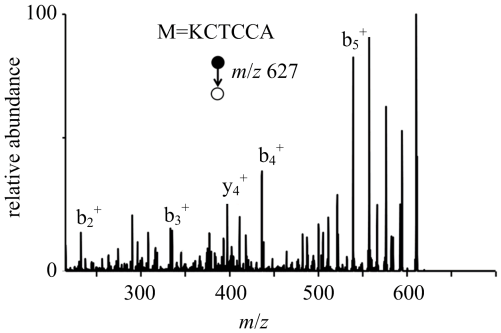
After proving migration and detection of dye on the μPADs, we then turned to test peptide samples in pure solution for rapid colorimetric screening coupled to MS measurement. The peptides (bradykinin (m/z 1 060.7), Ang II (m/z 1 032.7) and KCTCCA (m/z 628)) tested in this experiment were chosen as the model compounds for possible clinical applications, since peptide is a class of disease marker. According to the previous report[44], tetrabromophenol blue (TBPB) can bind with proteins in condition of proper solvent and pH, which will lead to a significant color change. And the depth of the color is related to the concentration of proteins. Firstly, chromogenic reagents were added to one of the detection zones by the way described above. Secondly, sample solution was added to the top layer of the μPADs and the sample was dried for 30 min. Lastly, the device was folded for contact of the first and secondary layers and CH_3OH/H_2O (volume ratio 3∶1, 10 μL) was added to elute the sample for three times. For the last step, peptides having migrated to MS detection zone were subjected to PS MS analysis. On-device images of bradykinin, Ang II and KCTCCA migration and associated MS detection are shown in Fig. 4. The positive result with a color change from yellow to blue is shown in Fig. 4(d), which was consistent with previous report[31]. It was reported that the chromogenic reagents can be used for protein detection[31]. Our result shows that this method can also be used for peptide detection. Per MS detection, Fig. 4(a) shows the characteristic fragment ions of b_6^+, y_8^+,



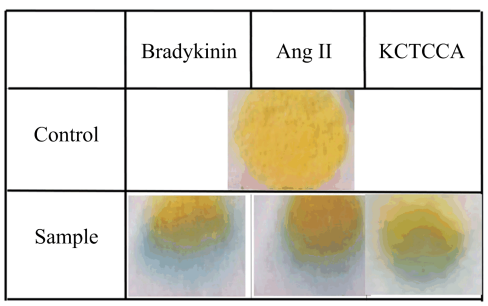
(a) The MS/MS spectra of bradykinin (500 μmol/L, 10 μL)



(b) The MS/MS spectra of angII (500 μmol/L, 10 μL)



(c) The MS/MS spectra of KCTCCA (500 μmol/L, 10 μL)



Chromogenic reagents are added onto the μPAD

(d) Colorimetric comparison of "controls" (pure solvent) and "samples" (500 μmol/L peptides)

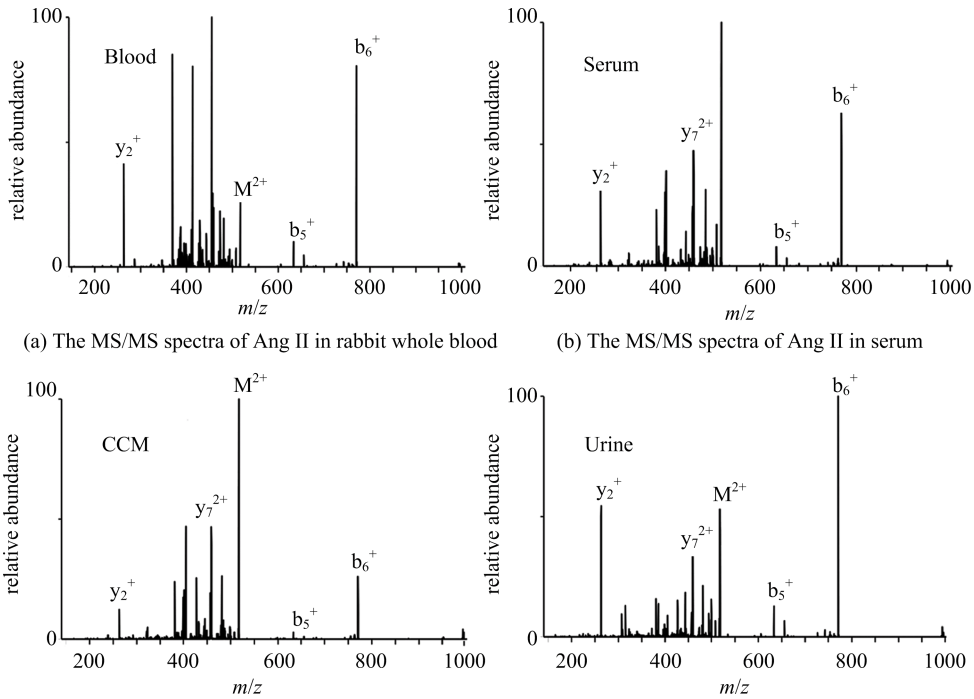
The MS/MS spectra of different peptides are presented ($MeOH/H_2O$ (volume ratio 3∶1) with the addition of 0.5% acetic acid as spray solvent).

Fig. 4 Peptide migration and MS detection

y_8^{2+}, etc. from double charged bradykinin (m/z 1 060.7). Fig. 4(b) shows characteristic fragment ions of y_2^+, b_6^+, b_5^+, etc. from double charged Ang II (m/z 1 032.7). Fig. 4(c) shows the characteristic fragment ions of b_2^+, b_3^+, b_5^+, etc. for protonated KCTCCA (m/z 628). According to the above results, it can be concluded that the colorimetric and PS MS detection are feasible for peptide detection in pure solution.

2.4 Combining colorimetric and MS detection in complex matrices

We further investigated the application of the present method to complex matrices other than pure samples. Four different matrices (rabbit whole blood, raw serum, CCM and raw urine) spiked with Ang II were tested. We chose Ang II as the model compound of peptides which represents a category of potential biomarkers. Firstly, Ang II (300 μmol/L, 10 μL) was spiked into these matrices without further treatment or dilution. Secondly, the sample solution was analyzed with colorimetric and MS detection. The results are illustrated in Fig. 5. The characteristic fragment ions of y_2^+, b_6^+, b_5^+, etc. are observed in

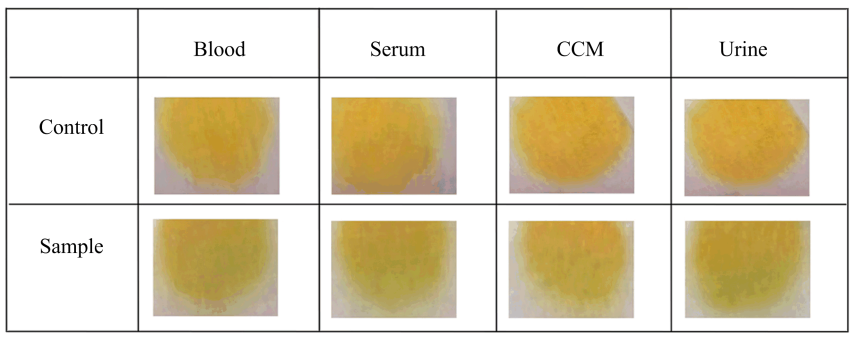


(a) The MS/MS spectra of Ang II in rabbit whole blood

(b) The MS/MS spectra of Ang II in serum

(c) The MS/MS spectra of Ang II in CCM

(d) The MS/MS spectra of Ang II in raw urine



Chromogenic reagents are added onto the μPAD

(e) The colorimetric comparison of "controls" to "samples" (300 μmol/L Ang II)

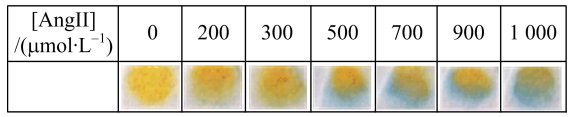
The MS/MS spectra of Ang II (300 μmol/L, 10 μL) is presented (MeOH/H_2O (volume ratio 3∶1) with the addition of 0.5% acetic acid as spray solvent in different matrices)

Fig. 5　Colorimetric and MS qualitative analysis in complex matrices

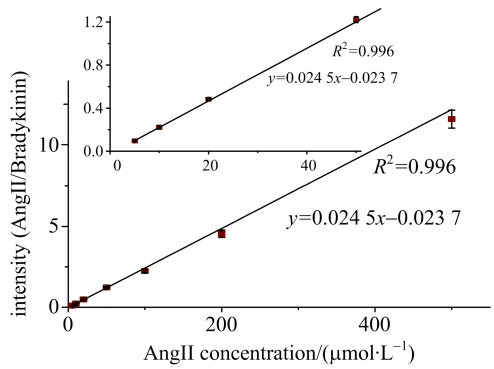
the MS/MS spectra corresponding to the Ang II. For Ang II (300 μmol/L, 10 μL) in complex matrices, slight color changes compared to the "controls" can be distinguished with the naked eye for all four matrices as shown in Fig. 5(e). It should be noted that, though tetra bromophenol blue was generally used as chromogenic reagent for total protein assay, the "controls" did not present the blue color. Due to the paper chromatography effect of the μPAD presented in this manuscript, when whole blood, serum and CCM were tested, the migration speed of the interferences (the proteins in the biological matrices) can be much slower than the small peptides such as spiked Ang II, which can also prevent those large proteins from reaching detection zones in a short period of time. The results showed that online colorimetric detection in μPADs may potentially be applied to fast screening peptides from complex matrices, and online MS detection with lower detection limit and high sensitivity and selectivity can be further used for final identification. If a more specific and sensitive method is used, the sensitivity of the colorimetric assay may be greatly improved. Thus, our research provides a convenient and sensitive method for assay of disease markers and other significant analytes.

2.5 Colorimetric and MS quantification

To study the analytical performances of the present method, colorimetric and MS quantification of Ang II in raw serum were studied. On-device images of colorimetric detection and associated calibration curves for MS detection of Ang II are shown in Fig. 6. For colorimetric detection, Ang II solutions with different concentrations (10 μL) were added to the top layer of the μPADs. The resulting linear range of 200～1 000 μmol/L was established for Ang II, and the visual detection limit was in the range of 150～200 μmol/L. For MS detection, solutions spiked with different concentrations of Ang II (100 μmol/L Bradykinin as internal standard) were added to the top layer of the device. Associated calibration



Chromogenic reagents are preloaded.
(a) Colorimetric detection of 200～1 000 μmol/L Ang II



The error bars represent the standard deviation of three replicate measurements at different concentrations. Inset plots are magnifications of lower part of the linear dynamic curves. MeOH/H_2O (volume ratio 3:1) with the addition of 0.5% acetic acid is used as spray solvent.
(b) MS/MS detection of 5~500 μmol/L Ang II with 100 μmol/L bradykinin as internal standard

Fig. 6 Colorimetric and MS Quantification

curves for Ang II are shown in Fig. 6(b). The resulting linear range of 5 ～ 500 μmol/L was established for Ang II, and LOD (limit of detection) of 1.90 μmol/L (experimentally measured as the amount at which the signal-to-noise ratios (S/N) was >3, with relative standard deviation RSD in the range of 3% ～ 20%) achieved. The spray maintained stable for about 5 min. During field analysis, colorimetric detection is easy to operate, which would benefit sample cutoff. For example, if the concerned concentration range for the analyte is below 500 μmol/L, the samples with obvious color change above 500 μmol/L can be excluded. Then the suspicious samples can be brought to lab for final MS identification, which is far more sensitive and selective than colorimetric detection. Besides, for patients' preliminary diagnosis at home the present method would save a lot of time. Colorimetric screening can be used for preliminary diagnosis and MS could be used for more sensitive diagnosis. Although specificity and sensitivity of the colorimetric detection used in this study was much

lower than the followed MS detection, with a more specific and sensitive colorimetric detection system[45-46] or introduction of magnification method[47], the present method would be very helpful for field analysis to increase instrument efficiency and decrease cost for sample transportation.

3 Conclusion

In summary, a novel μPAD was developed for easy and rapid screening prior to MS analysis of peptides. This proof-of-principle protocol was proved via two steps: ① detection of peptides in pure solvent and ② detection of peptides in complex matrices (rabbit whole blood, raw serum, CCM and raw urine). In all these experiments, the μPAD served as sample collector, sample splitter and substrate for colorimetric screening and PS MS analysis. Colorimetric detection was used for sample cut-off or preliminary diagnosis and MS was used for sensitive analysis. The results indicate that the present method is helpful for field analysis to increase instrument efficiency and decrease cost for sample transportation. Besides, the present method may also be used for cheap versions of point-of-care pharmaceutical treatment at home to provide a simple and fast prior diagnosis, which is particularly useful for the people in extremely poor countries and areas.

References

[1] HARRIS G A, GALHENA A S, FEMANDEZ F M. Ambient sampling/ionization mass spectrometry: Applications and current trends[J]. Anal Chem, 2011, 83(12): 4 508-4 538.

[2] GRIFFITHS W J, WANG Y. Mass spectrometry: From proteomics to metabolomics and lipidomics[J]. Chem Soc Rev, 2009, 38(7): 1 882-1 896.

[3] ZHENG J, SUGRUE R J, TANG K. Mass spectrometry based proteomic studies on viruses and hosts--a review[J]. Anal Chim Acta, 2011, 702(2): 149-159.

[4] MAGI E, TANWAR S. "Extreme mass spectrometry": The role of mass spectrometry in the study of the Antarctic environment [J]. J Mass Spectrom, 2014, 499(11): 1 071-1 085.

[5] GAO L, SUGIARTO A, HARPER J D, et al. Design and characterization of a multisource hand-held tandem mass spectrometer[J]. Anal Chem, 2008, 80(19): 7 198-7 205.

[6] LI L, CHEN T C, REN Y, et al. Mini 12, miniature mass spectrometer for clinical and other applications--introduction and characterization [J]. Anal Chem, 2014, 86(6): 2 909-2 916.

[7] HENDRICKS P I, DALGLEISH J K, SHELLEY J T, et al. Autonomous in situ analysis and real-time chemical detection using a backpack miniature mass spectrometer: Concept, instrumentation development, and performance[J]. Anal Chem, 2014, 86(6): 2 900-2 908.

[8] BADMAN E R, COOKS R G. Miniature mass analyzers[J]. J Mass Spectrom, 2000, 35: 659-671.

[9] OUYANG Z, COOKS R G. Miniature mass spectrometers[J]. Annu Rev Anal Chem, 2009, 2: 187-214.

[10] TAKÁTS Z, WISEMAN J M, GOLOGAN B, et al. Mass spectrometry sampling under ambient conditions with desorption electrospray ionization [J]. Science, 2004, 306(5695): 471-473.

[11] EWING K J, GIBSON D, SANGHERA J, et al. Desorption electrospray ionization-mass spectrometric analysis of low vapor pressure chemical particulates collected from a surface[J]. Anal Chim Acta, 2015, 853: 368-374.

[12] TAKÁTS Z, WISEMAN J M, COOKS R G. Ambient mass spectrometry using desorption electrospray ionization (DESI): Instrumentation, mechanisms and applications in forensics, chemistry, and biology[J]. J Mass Spectrom, 2005, 409(10): 1 261-1 275.

[13] CODY R B, LARAMÉE J A, DURST H D. Versatile new ion source for the analysis of materials in open air under ambient conditions [J]. Anal Chem, 2005, 77(8): 2 297-2 302.

[14] WANG Y, LI C, HUANG L, et al. Rapid identification of traditional Chinese herbal medicine by direct analysis in real time (DART) mass spectrometry [J]. Anal Chim Acta, 2014, 845: 70-76.

[15] CHEN H, VENTER A, COOKS R G. Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation[J]. Chem Commun, 2006, 19: 2 042-2 044.

[16] LI X, FANG X, YU Z, et al. Direct quantification of creatinine in human urine by using isotope dilution extractive electrospray ionization tandem mass

spectrometry[J]. Anal Chim Acta, 2012, 748:53-57.
[17] LIU Y, ZHANG X, OUYANG Y, et al. Trace detection of hormones and sulfonamides in viscous cosmetic products by neutral desorption extractive electrospray ionization tandem mass spectrometry[J]. J Mass Spectrom, 2011, 46(8):794-803.
[18] WALWORTH M J, STANKOVICH J J, VAN BERKEL G J, et al. Hydrophobic treatment enabling analysis of wettable surfaces using a liquid microjunction surface sampling probe/electrospray ionization-mass spectrometry system[J]. Anal Chem, 2011, 83(2):591-597.
[19] WANG H, LIU J, COOKS R G, et al. Paper spray for direct analysis of complex mixtures using mass spectrometry[J]. Angew Chem Int Ed, 2010, 49(5): 877-880.
[20] ZHANG Y, JU Y, HUANG C, et al. Paper spray ionization of noncovalent protein complexes[J]. Anal Chem, 2014, 86(3):1 342-1 346.
[21] DENG J, YANG Y. Chemical fingerprint analysis for quality assessment and control of Bansha herbal tea using paper spray mass spectrometry[J]. Anal Chim Acta, 2013, 785:82-90.
[22] GALUSZKA A, MIGASZEWSKI Z M, NAMIEŠNIK J. Moving your laboratories to the field: Advantages and limitations of the use of field portable instruments in environmental sample analysis[J]. Environmental research, 2015, 140: 593-603.
[23] LIANA D D, RAGUSE B, GOODING J J, et al. Recent advances in paper-based sensors[J]. Sensors, 2012, 12(9):11 505-11 526.
[24] LI X, BALLERINI D R, SHEN W. A perspective on paper-based microfluidics: Current status and future trends[J]. Biomicrofluidics, 2012, 6:11 301-11 314.
[25] SAMEENOI Y, NONGKAI P N, NOUANTHAVONG S, et al. One-step polymer screen-printing for microfluidic paper-based analytical device (muPAD) fabrication[J]. The Analyst, 2014, 139(24):6 580-6 588.
[26] COLTRO W K T, CHENG C M, CARRILHO E, et al. Recent advances in low-cost microfluidic platforms for diagnostic applications[J]. Electrophoresis, 2014, 35(16):2 309-2 324.
[27] COLTRO W K T, DE JESUS D P, DA SILVA J A F, et al. Toner and paper-based fabrication techniques for microfluidic applications[J]. Electrophoresis, 2010, 31(15):2 487-2 498.
[28] NERY E W, KUBOTA L T. Sensing approaches on paper-based devices: A review[J]. Anal Bioanal Chem, 2013, 405(24):7 573-7 595.
[29] SANTHIAGO M, HENRY C S, KUBOTA L T. Low cost, simple three dimensional electrochemical paper-based analytical device for determination of p-nitrophenol[J]. Electrochim Acta, 2014, 130: 771-777.
[30] DELANEY J L, DOEVEN E H, HARSANT A J, et al. Use of a mobile phone for potentiostatic control with low cost paper-based microfluidic sensors[J]. Anal Chim Acta, 2013, 790:56-60.
[31] MARTINEZ A W, PHILLIPS S T, WHITESIDES G M. Three-dimensional microfluidic devices fabricated in layered paper and tape[J]. Proc Natl Acad Sci, 2008, 105(50):19 606-19 611.
[32] MARTINEZ A W, PHILLIPS S T, BUTTE M J, et al. Patterned paper as a platform for inexpensive, low-volume, portable bioassays[J]. Angew Chem Int Ed, 2007, 46(8):1 318-1 320.
[33] NIE Z, NIJHUIS C A, GONG J, et al. Electrochemical sensing in paper-based microfluidic devices[J]. Lab on A Chip, 2010, 10(4):477-483.
[34] LIU H, CROOKS R M. Three-dimensional paper microfluidic devices assembled using the principles of origami[J]. J Am Chem Soc, 2011, 133(44):17 564-17 566.
[35] FOSDICK S E, ANDERSON M J, RENAULT C, et al. Wire, mesh, and fiber electrodes for paper-based electroanalytical devices[J]. Anal Chem, 2014, 86(7): 3 659-3 666.
[36] SCIDA K, LI B, ELLINGTON A D, et al. DNA detection using origami paper analytical devices[J]. Anal Chem, 2013, 85(20):9 713-9 720.
[37] EVANS E, GABRIEL E F M, COLTRO W K T, et al. Rational selection of substrates to improve color intensity and uniformity on microfluidic paper-based analytical devices[J]. The Analyst, 2014, 139(9): 2 127-2 132.
[38] MU X, XIN X, FAN C, et al. A paper-based skin patch for the diagnostic screening of cystic fibrosis[J]. Chem Commun, 2015, 51(29):6 365-6 368.
[39] DUNGCHAI W, CHAILAPAKUL O, HENRY C S. Use of multiple colorimetric indicators for paper-based microfluidic devices[J]. Anal Chim Acta, 2010, 674(2):227-233.
[40] JAYAWARDANE B M, WET S, MCKELVIE I D, et al. Microfluidic paper-based analytical device for the determination of nitrite and nitrate[J]. Anal Chem, 2014, 86(15):7 274-7 279.
[41] KARITA S, KANETA T. Acid-base titrations using microfluidic paper-based analytical devices[J]. Anal Chem, 2014, 86(24):12 108-12 114.

[42] KUMAR A, HENS A, ARUN R K, et al. A paper based microfluidic device for easy detection of uric acid using positively charged gold nanoparticles[J]. The Analyst, 2015, 140(6):1 817-1 821.

[43] LIU W, LIN J. Online monitoring of lactate efflux by multi-channel microfluidic chip-mass spectrometry for rapid drug evaluation[J], ACS Sensors, 2016,1(4): 344-347.

[44] PUGIA M J, LOTT J A, PROFITT J A, et al. High-sensitivity dye binding assay for albumin in urine[J]. Journal of Clinical Laboratory Analysis, 1999, 13:180-187.

[45] LI M, CAO R, NILGHAZ A, et al. "Periodic-table-style" paper device for monitoring heavy metals in water[J]. Anal Chem, 2015, 87(5): 2 555-2 559.

[46] WEAVER A A, REISER H, BARSTIS T, et al. Paper analytical devices for fast field screening of beta lactam antibiotics and antituberculosis pharmaceuticals [J]. Anal Chem, 2013, 85(13): 6 453-6 460.

[47] TSAI T T, Shen S W, CHENG C M, et al. Paper-based tuberculosis diagnostic devices with colorimetric gold nanoparticles[J]. Sci Technol Adv Mater, 2013, 14(4): 044404-044411.

(上接第 820 页)

[13] 金建忠,童建颖. 超临界 CO_2 萃取杭白菊挥发油的工艺研究 [J]. 食品科学,2010,31(14): 125-127.
JIN Jianzhong, TONG Jianying. Supercritical carbon dioxide extraction of volatile oil from Chrysanthemum morifolium [J]. Food Science, 2010, 31 (14): 125-127.

[14] WU X, LEUNG D Y C. Optimization of biodiesel production from camelina oil using orthogonal experiment [J]. Applied Energy, 2011, 88 (11): 3 615-3 624.

[15] DÍAZ-MAROTO M C, PEREZ-COELLO M S, CABEZUDO M D. Supercritical carbon dioxide extraction of volatiles from spices: comparison with simultaneous distillation-extraction [J]. Journal of Chromatography A, 2002, 947(1): 23-29.

[16] XIAO Z, FAN B, NIU Y, et al. Characterization of odor-active compounds of various Chrysanthemum essential oils by gas chromatography-olfactometry, gas chromatography-mass spectrometry and their correlation with sensory attributes [J]. Journal of Chromatography B, 2016, 1009(12): 152-162.