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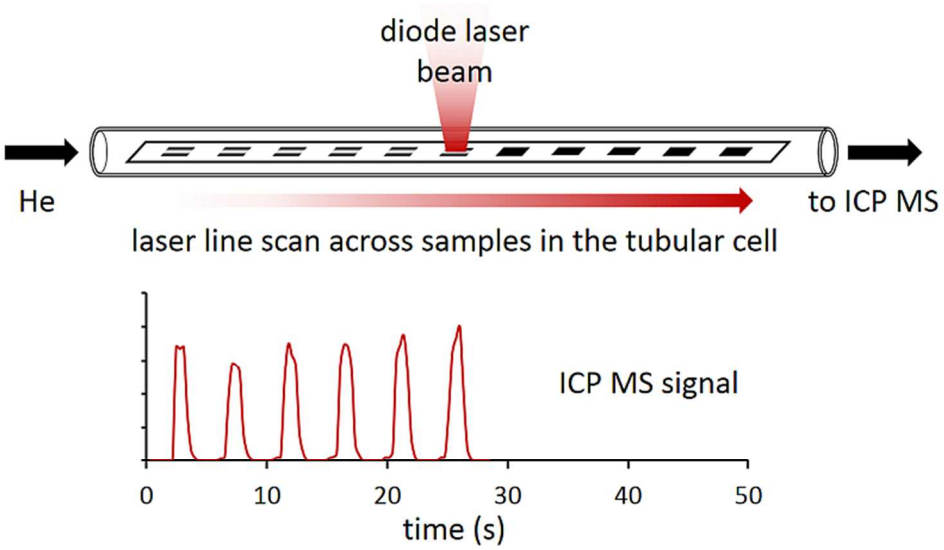

Low-cost diode laser thermal vaporization sample introduction system to ICP MS for determination of lead and cadmium in whole blood
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ARTICLE

Diode laser thermal vaporization ICP MS with a simple tubular cell for determination of lead and cadmium in whole blood

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A new low-cost device suitable for the recently presented sample introduction technique to inductively coupled plasma mass spectrometry (ICP MS), diode laser thermal vaporization (DLTV), is described. DLTV ICP MS is suitable for quantitative elemental analysis of low volume liquid samples and offers an alternative to commonly used liquid sample introduction into inductively coupled plasma. In contrast to existing sample introduction systems based on laser ablation, the technique relies on low-cost components: a diode laser, a simple laboratory-built cell and a strip of filter paper. The aerosol generation by DLTV is carried out in a simple cell made up of a glass tube, a near infrared continuous-wave diode laser and a common syringe pump. The cell is characterized by minimal dead volume, which reduces turbulent flow and provides very fast wash-out. The paper substrate can hold up to 24 samples; analysis time per sample ~4.7 s has been achieved. The device performance was optimized, compared to a commercial ablation system and applied to the determination of lead and cadmium in whole human blood without any sample treatment. A prearranged calibration set was printed on the paper strip using a piezoelectric dispenser.

Introduction

Exposure to toxic trace elements, such as lead and cadmium, has been recognized as an environmental problem for decades. Determination of these elements in human blood is important for exposure assessment of an individual. Whole blood lead concentrations above 300 $\mu g.L^{-1}$ in adults indicate significant exposure; recent studies suggest evidence of adverse health effects in children for lead concentrations as low as 100 $\mu g.L^{-1}$.[1] Cadmium is classified as a human carcinogen and whole blood level of 5 $\mu g.L^{-1}$ or higher is considered hazardous.[2,3]

The determination of lead and cadmium in biological materials is demanding mainly due to low concentrations of both metals and a complex matrix varying from sample to sample. Analytical methods used for lead or cadmium determination in liquid blood include electrothermal atomic absorption spectrometry (ETAAS),[4,5] hydride generation atomic fluorescence spectrometry (HG AFS),[6,7] anodic stripping voltammetry techniques[8,9] and inductively coupled plasma mass spectrometry (ICP MS).[10,11] ICP MS is a highly sensitive technique for the determination of trace elements but the analysis of liquid blood sample is limited due to possible contamination and impurities introduced during sample pretreatment processes such as an extraction, dilution or microwave-assisted digestion. These conventional ICP MS methods usually require several milliliters of collected blood fixed with appropriate conserving mixtures immediately after sampling and stored at a low temperature.

An alternative approach for the assessment of metals uses dried blood spots on filter paper instead of liquid blood to speed up the analysis and reduce costs. Blood samples stored on filter paper are stable for at least six months.[12] Analysis of dried blood spots on filter paper typically involves some type of sample pretreatment such as extraction or ashing of the blood spot, cutout followed by flame or electrothermal atomic absorption spectrometry[13] or ICP MS analysis.[14] However, these pretreatment procedures can lead to incomplete recovery or contamination. Analysis of blood spots on filter paper by laser ablation (LA) ICP MS eliminates the risk of contamination because no sample pretreatment is required; the disadvantage is, however, a long acquisition time, almost 5 min per sample.[15,16]

Generation of an aerosol using a laser technique is carried out in an ablation cell. Characteristics of the cell affect the overall transport efficiency and the measured signal profile. Commercially available and commonly used are closed-design cylindrical cells with an inlet/outlet located on the sides and

with a glass window as the top face. The extraction efficiency lies between 5 and 15% depending on the volume, the inlet flow rate and the type of the carrier gas. These cells exhibit a symmetry axis orthogonal to the gas flow axis which induces vorticity and re-circulation and thus induces signal dispersion as a function of increasing cell size. The non-uniform flow causes varying sensitivity throughout the cell.[17] Improved designs of ablation cell were developed to maximize aerosol extraction efficiency and transport speed, but they are not commercially available.[18] A comparison of a standard cylindrical cell and a bottle-shaped cell showed that the "bottle" cell provided more than one order of magnitude higher sensitivity and lower detection limits, which was caused by different flow patterns across the two ablation cells.[19] Bleiner *et al.* developed a "piston cell"[20] made from a plastic syringe which had an extraction efficiency of 66% and an open-design tube cell[21] which provided the least dead volume possible. The reduction of the cell volume brings sharper signal peaks and more resolved depth-related information from the ablation process due to the reduced aerosol mixing between individual laser pulses. The concept of the simple linear cell[22] decreasing the rinse time down to tens of milliseconds is based on suppression of the gas turbulence and the ablation in the part of the cell with the laminar flow. The authors demonstrated a sharpening of peaks, which improves the signal-to-noise ratio and minimizes the losses on walls. Presently, the most widely used ablation cell types, especially the cylindrical ones, are supplied by Cetac®[23] or New Wave Research®[24]. The other commercially available cells include SuperCell™, HelEx™ Cell, large format cells, document (paper) cells, frames cell or CryoCell and other. In comparison with the nebulizer systems, the ablation systems are at least 25-fold more expensive.

Piezoelectric dispensers based on the inkjet printing technology have gained popularity as precise micro-dispensing tools for handling submicroliter sample volumes. These dispensers are able to generate and deposit droplets with a distinct volume ranging down to a few picoliters (±1–3% size variation) onto various substrates by noncontact printing.[25] To create a droplet, a volumetric change in the fluid is induced by the application of a voltage pulse to a piezoelectric material that is coupled, directly or indirectly, to the fluid. This volumetric change causes pressure/velocity transients to occur in the fluid and these are directed so as to eject the droplet that issues from an orifice.[26] Using the optimized voltage pulse waveform, the ejected droplets have diameters approximately the same size as the nozzle orifice.[25] A similar technique employing a thermal dispenser was developed as a promising method for sample preparation and calibration of LA ICP TOF MS.[28]

Recently, we introduced a new sample introduction method for ICP MS - diode laser thermal vaporization (DLTV) employing a low-cost continuous-wave diode laser instead of a pulse Nd:YAG laser.[27] Laser power is sufficient to induce pyrolysis of a suitable substrate with a deposited sample leading to aerosol generation. The method was used for quantitative determination of metals in submicroliter liquid samples. Applicability was demonstrated on determination of lead in whole blood, which was performed by depositing 200-nL blood droplets on common office paper with preprinted squares without any sample pretreatment.

Here, we present a novel simple device designed for DLTV which replaces the commercial laser ablation system. The device is constructed using a common syringe pump which moves the diode laser along a cell made of a glass tube. The performance of DLTV ICP MS with the new cell is demonstrated on the determination of lead and cadmium in human whole blood using a prearranged multi-elemental calibration set deposited with a piezoelectric dispenser.

Experimental

Chemicals

Stock solution, certified reference material (Analytika, Czech Republic) containing 100 mg.L^{-1} Pb and 100 mg.L^{-1} Cd in 5 % nitric acid and 0.2 % hydrofluoric acid was used as a standard for ICP MS. Human blood (BCR-634, Sigma-Aldrich, Czech Republic) certified by the Community Bureau of Reference was used as a sample.

Sample preparation

Rectangles with dimensions 2.6 × 1.2 mm (length × width) with spacing 1.9 and 1.8 mm, respectively, were printed using black ink (HP CB316E, Hewlett Packard, Ireland) onto filter paper (Munktell quant 389, Germany) by an inkjet printer (HP Photosmart C5380). Samples were deposited on the preprinted rectangles as 200-nL droplets by a micropipette (2.5 µL, Biohit, Proline) or as a defined number of droplets using a single jet piezoelectric dispenser with a 50 µm orifice MJ-ABP-01-50-DLC (MicroFab Technologies, Texas, USA). Inaccuracy and imprecision of the micropipette for the testing volume 250 nL are 12 % and 6 % according to the manufacturer's specifications. For analysis in the tubular cell, the width of the paper strip, cut out of the filter paper sheet, was 3.0 mm; the strip length was up to 105 mm (corresponding to 24 rectangles) according to the desired number of analyzed samples. In the commercial system (SuperCell™, laser ablation system UP 213, New Wave Research, Inc., Fremont, CA, USA), a paper sheet with an array of 3 × 3 rectangles of the same size was used.

For piezoelectric deposition, the dispenser was mounted on an arm of a three-dimensional xyz robotic positioning device equipped with the three linear motorized stages (8MT-175-100, Standa Ltd, Vilnius, Lithuania). The voltage waveform for the dispenser was generated using a laboratory-built driver controlled with a LabVIEW program. The optimized symmetric double-pulse waveform with a positive and a negative wave was applied to the dispenser piezoelement at frequency 200 Hz. The liquid reservoir made of a 1-mL plastic pipetting tip was mounted on the rack so that the level of liquid was 10 mm under the position of the dispenser tip. The volume of a single droplet was calculated to be 65 pL. Thus, a droplet of 1-mg.L^{-1} standard solution contains 0.065 pg of Pb and Cd. If not stated

otherwise, a series of 20-pg samples was deposited on the paper strip using the piezoelectric dispenser as 307 droplets of 1-mg.L^{-1} standard solution.

Cell design

The paper strip was inserted into the 170-mm long glass tube with i.d. 3.8 mm and o.d. 6.0 mm, see Fig. 1. The glass tube was fixed between gas-in and gas-out valve ports using polyether polyurethane tube (Legris, France). A continuous-wave 808-nm diode laser module (RLDH808-1200-5, Roithner LaserTechnik, Austria) was attached to the slider of a syringe pump (NE-1010, New Era Pump Systems, USA), which served as the translational stage for the line scan of the laser beam along the paper strip. The power of the diode laser was found to be 1.08 W after a 30-min warm-up period. If not stated otherwise, the laser beam scan speed was 0.95 mm.s^{-1}.

For analyses in the commercial cell, the diode laser was attached to the ablation system using an aluminum holder and the built-in Nd:YAG laser was turned off.

Fig. 1 Photograph of the laboratory-built device for DLTV

ICP MS

The generated aerosol was transported by a carrier gas (helium) at flow rate 0.8 L min^{-1} from the cell to an ICP MS, model 7500CE (Agilent Technologies, Inc., Santa Clara, CA, USA). A sample gas flow of argon (0.6 L.min^{-1}) was mixed with the helium carrier gas flow subsequent to the cell. The ion signals of ^{208}Pb, ^{111}Cd and ^{13}C isotopes were recorded with an integration time 0.1 s/isotope. The ^{13}C ion signal was monitored to indicate the pyrolysis of paper and to set the interval for integration of the Pb and Cd ion signals accordingly.

Results and discussions

Laser position and focusing

The laser beam scanned along the paper strip in the tubular cell. When the beam moved to a preprinted rectangle, the ink absorbed laser irradiation inducing pyrolysis of the paper and generating the metal-containing aerosol. After the beam left the rectangle, the pyrolysis ceased and the ICP MS signal dropped. Movement of the beam between the rectangles did not induce pyrolysis and it served for the cell wash-out.

Dependence of the signal intensities of Pb and Cd in combination with the vertical laser distance from the paper strip and laser focusing was examined in order to choose the optimal experimental arrangement. The integrated signal from ten 20-pg samples and control samples was monitored at the distances 25; 35; 45; 55 and 65 mm from the paper strip with various focal points. The preprinted rectangles without deposited samples were used as control samples. An integrated signal of ^{13}C, ^{208}Pb and ^{111}Cd, integrated ^{208}Pb/^{13}C and ^{111}Cd/^{13}C signal ratios, signal (integrated isotope/^{13}C signal ratio of sample) to noise (integrated isotope/^{13}C signal ratio of control sample) ratio (*S*/*N*), spot to spot reproducibility (RSD) were evaluated.

Thermal vaporization was observed with the focal point ranging from ~10 mm above to ~10 mm below the paper strip at the distances 25 and 35 mm from the strip, from ~5 mm above to ~5 mm below the paper strip at the distances 45 and 55 mm and only directly at the focus on the paper strip at the distance 65 mm. The diode laser showed astigmatism and thus the shape and size of the laser spot depended on focusing. The shape of the laser spot for focusing above or below the paper strip was elliptic; focusing directly on the paper strip resulted in roughly a circular shape of the beam with a diameter ~0.8 mm. The laser was turned by 90° in order to maintain the longer part of the ellipse perpendicular to the longer side of the rectangle (and scan trajectory) at distances ≥45 mm from the paper strip. Focusing the laser beam right on the preprinted paper strip resulted in burnout of the paper at all tested distances of the laser whereas focusing above or below the paper strip caused burning of the surface ink layer only.

The integrated ICP MS signal was found to increase with the higher vaporized amount of substrate by visual inspection. This effect was observed for the integrated ICP MS signal of both isotopes as well as for the integrated isotope to ^{13}C signal ratio for both metal and control samples. It should be pointed out that the paper strips should be checked for heterogeneities and curvatures as they could affect the vaporization process and signal intensities.

The highest *S*/*N* values of integrated signals of the both Pb and Cd isotopes were achieved at a distance of 35 mm above and focusing ~8 mm below the paper strip (48 for ^{208}Pb and 1100 for ^{111}Cd) and isotope/^{13}C ratio at a distance of 45 mm above and focusing ~8 mm below the paper strip (22 for ^{208}Pb and 720 for ^{111}Cd). It was observed that the burnout of paper also increased RSD. The minimal RSD was achieved at a distance of 45 mm above and focusing 5 mm below the paper strip (5% for ^{208}Pb/^{13}C) and at a distance of 35 mm and focusing ~8 mm below the paper strip (7% for ^{111}Cd/^{13}C).

Based on the observations, the laser position 35 mm above the paper strip and focusing ~8 mm below the strip was selected as a compromise for both the monitored isotopes. In this arrangement, the laser spot was elliptic with major axis 1.2 mm and minor axis 1.0 mm.

Cell volume

The total amount of aerosol transported and signal dispersion are a function of the cell volume. In the laser ablation process, the extreme reduction of cell volume can cause the laser-

generated plume to spatter onto the cell wall, which leads to a partial loss of aerosol and longer rinse times. The influence of the cell volume on rise and rinse times and *S*/*N* was studied on a series of 20-pg samples. Control samples were preprinted rectangles without the deposited samples. The samples were vaporized under similar conditions in the laboratory-built and the commercial cells. To achieve as similar conditions as possible in the both cells, the laser was focused on the paper strip from a distance of 65 mm and the laser scan speed was 0.95 mm.s^{-1}. The laser beam incidence angle was set to 30° because the diode laser could not be positioned perpendicular to the paper strip as in the commercial cell. The volume of the laboratory-built cell is 1.9 cm^3 and the volume of the commercial cell is 33 cm^3.

As can be seen in Table I, analysis of nine replicates of 20-pg samples in the laboratory-built cell showed a similar ^{208}Pb/^{13}C signal ratio (5.4±1.5)×10^{-4} as the analysis of the nine replicates in the commercial cell (6.2±1.0)×10^{-4}, whereas the ^{111}Cd/^{13}C signal ratio showed three-fold higher values for the laboratory-built cell (6±4)×10^{-4} than the analysis in the commercial cell (2.2±1.1)×10^{-4}. It was observed that the isotope/blank ratio doubled in the case of the laboratory-built cell. The rise time was calculated as the time between the first point of the signal peak and the highest point of the peak. The rinse time was calculated as the time between the highest point of the peak and the point of the peak where the signal dropped below 5% of the signal maximum. The rise time was similar for both cells, whereas the rinse time was significantly shorter in the case of the laboratory-built cell as shown in Fig. 2.

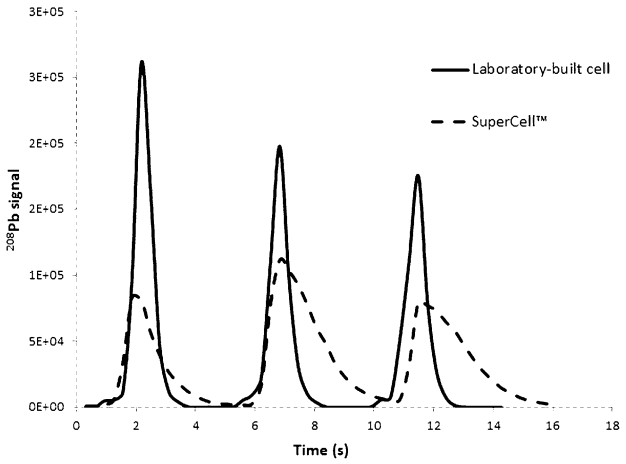

Fig. 2 Comparison of the ^{208}Pb signal peak profiles in the commercial SuperCell™ and the laboratory-built tubular cell

Table I shows the overall comparison of cell characteristics. It was found that the reduction of the laboratory-built cell volume didn't cause aerosol loss and the reduction of volume led to a decreasing rinse time in comparison with the commercial cell.

Table I Comparison of the laboratory-built and the commercial cells

	Laboratory-built cell		SuperCell™	
Volume	1.9 cm^3		33 cm^3	
Isotope	^{208}Pb	^{111}Cd	^{208}Pb	^{111}Cd
Rise time [s]	1.5	1.2	1.3	1.2
Rinse time [s]	1.2	1.2	3.0	1.9
Integrated isotope/^{13}C signal ratio of 20-pg samples (×10^{-4})	5.4±1.5	6.1±0.4	6.2±1.0	2.2±0.2
Integrated isotope/^{13}C signal ratio of blank (×10^{-6})	39±8	5±1	95±3	3±2
The height/width ratio	14	1200	7	700

Cell shape

The most widely used shape of the cell is cylindrical. This shape can induce vorticity and re-circulation of the gas flow which can cause non-uniform sensitivity throughout the cell. The tubular shape of the cell can create a more uniform gas flow pattern inside the cell and minimize internal gas circulation. It can lead to the same aerosol transport efficiency regardless of the sampling position and thus to unify sensitivity throughout the cell. In contrast to the commercial cell, the paper strip was placed into the cell loosely without any support allowing gas flow on the both sides of the strip. In order to investigate the tubular cell performance, a series of ten samples, each containing 20 pg of both metals, deposited on the paper strip within the preprinted pattern. No signal decrease or increase in dependence on sample position was observed. The ^{208}Pb/^{13}C and ^{111}Cd/^{13}C signal ratios showed similar values for a sample placed close to the gas inlet (6.0×10^{-5}; 2.9×10^{-4}), in the middle position of the tube (6.3×10^{-5}; 2.8×10^{-4}) as well as close to the gas outlet (5.9×10^{-5}; 2.7×10^{-4}). Although the direction of the laser scan was the same as that of the gas flow, no sample cross-contamination was observed.

Laser scan speed

The total analysis time is mainly influenced by linear laser scan speed. In order to find the maximum laser scan speed without any undesirable effects, ion signal from a series of 20 pg samples was recorded at five values of laser scan speeds: 0.7; 0.95; 1.17; 1.6 and 2.1 mm.s^{-1}.

Integrated ^{208}Pb/^{13}C signal ratio showed the maximum values for 1.6 and 2.1 mm.s^{-1} with RSD 10 and 27%, respectively. However, integrated ^{111}Cd/^{13}C signal ratio exhibited maximum values for laser scan speed 0.95 and 1.17 mm.s^{-1} with RSD 5 and 9%, respectively. This difference corresponds to the observations described in the paragraph Laser position and focusing. The ion signal of ^{13}C was found to increase with the growing laser scan speed. The maximum laser speed that allowed the ion signals of the analyzed isotopes to

drop to the baseline between the adjacent samples was 0.95 mm.s^{-1}. This laser scan speed was chosen for further experiments.

Limits of detection and reproducibility

In order to determine limits of detection of Pb and Cd, 2-nL volumes of 1-mg.L^{-1} standard solution (31 droplets; 2 pg of Pb and Cd) were deposited by piezoelectric dispenser on preprinted paper and vaporized in three replicates. LOD calculated from a peak area was 0.5 pg Pb and 0.02 pg Cd.

To investigate spot-to-spot signal reproducibility a series of 20-nL droplets of 1-mg.L^{-1}, standard solution (307 droplets; 20 pg of Pb and Cd) was deposited by piezoelectric dispenser on the paper strip with preprinted patterns. Analysis of ten replicates showed spot-to-spot RSD of integrated ion signals of ^{208}Pb and ^{111}Cd 40% and 10%, respectively. Correction on ^{13}C significantly reduced deviations caused by paper inhomogeneity and curvature of the paper strip; the RSD values for ^{208}Pb/^{13}C and ^{111}Cd/^{13}C signal ratios were 25% and 8%, respectively.

Prearranged multi-elemental calibration sets

An attractive option of DLTV is employment of prearranged calibration sets for multi-elemental calibration. These calibration sets can be prepared in advance and archived. Deposition by piezoelectric dispenser allows regulating the total amount of deposited standard solution down to a few nanoliters. Moreover, utilizing the dispenser minimizes the risk of contamination and errors by dilution during preparation of the multi-elemental calibration sets because the deposited amounts are regulated by the numbers of droplets of a single concentrated solution standard rather than by using solutions of different concentrations. Finally, deposition of the sample solution on all spots in the calibration set allows application of multiple standard addition technique.

In order to investigate calibration linearity, 3; 15; 31; 77; 154 and 770 droplets of 10-mg.L^{-1} Pb and Cd standard solution, i.e. 2; 10; 20; 50; 100 and 500 pg, were deposited on the paper strip in three replicates. Ion signal ratios (related to ^{13}C) were evaluated to minimize distortions produced by inhomogeneities and curvature of the paper strip. The calibration plots showed linearity within the examined range with the coefficient of determination higher than 0.967 for both the tested metals.

Determination of Pb and Cd in whole human blood

Lead and cadmium in whole blood were determined in the certified reference material BCR-634 (human blood) which contains 46±5 μg.L^{-1} of Pb and 1.4±0.4 μg.L^{-1} of Cd using the multiple standard addition technique to eliminate the matrix effect. A prearranged multi-elemental calibration set consisted of three concentration levels in three replicates (40, 10, 2 pg of Pb and 10, 2 and 1 of Cd) and six blank spots. Blood droplets of 200-nL volume were deposited on the preprinted rectangles with the calibration solutions and the blank rectangles in three replicates. The other three remaining blank preprinted patterns were used as the control samples. The ion signal of ^{208}Pb and ^{111}Cd was recorded under the optimized experimental conditions; the trace for ^{208}Pb is shown in Fig. 3. The determined content was 47±4 μg.L^{-1} for Pb and 1.7±0.6 μg.L^{-1} for Cd.

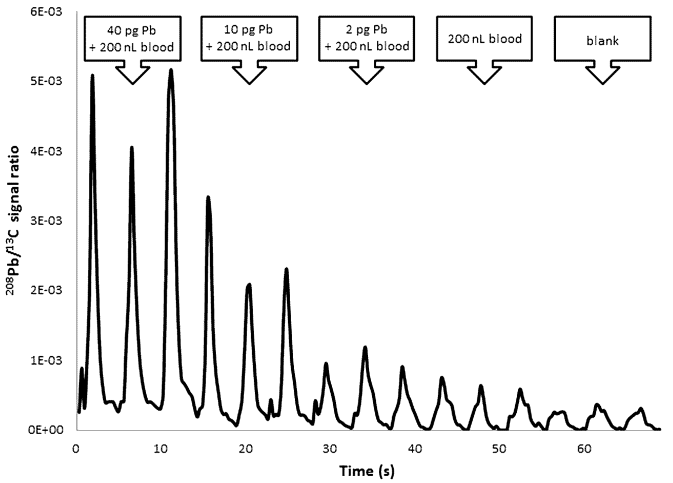

Fig. 3 Time record of a line scan along the paper strip for determination of Pb in whole blood

Conclusion

A new low-cost system for DLTV sample introduction to inductively coupled plasma has been constructed, tested and optimized. The laboratory-built device was made up of equipment commonly available in an analytical laboratory: a glass tube and syringe pump. A near infrared continuous-wave diode laser was employed rather than Nd:YAG pulse laser. Due to the low price of the utilized components, the device represents a suitable alternative to classical nebulizers for solution analysis.

The minimal dead volume of the cell reduces aerosol diffusion, enhances the transient signal aspect ratio and enables very fast wash-out of the cell. Comparison of the laboratory-built cell and a first-rate commercial ablation cell (SuperCell™) showed similar rise times of the signals. However, the laboratory-built cell produced higher height-to-width ratios and faster rinse times of the signal peaks compared to the commercial cell. The issue of diode laser position and focusing was not straightforward due to laser astigmatism; the laser position 35 mm above the paper strip and focusing ~8 mm below the strip was selected as a compromise suitable for both the monitored isotopes.

Laser scan speed was optimized; analysis time ~4.7 s per sample has been achieved. Advantageously, a piezoelectric dispenser was used to prepare a multi-elemental calibration set for DLTV ICP MS analysis. The paper strips with standards and/or samples can be easily archived and transported. The approach was demonstrated on the determination of lead and cadmium in whole blood. The whole blood was simply deposited without any pretreatment on a prearranged standard

set prepared with the piezoelectric dispenser and analyzed by DLTV ICP MS using the laboratory-built device.

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