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Rapid detection of aflatoxin B1, zearalenone and ochratoxin A in grains by thermal desorption dielectric barrier discharge ionization mass spectrometry

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Dielectric barrier discharge ionization is increasingly used for rapid detection in ambient mass spectrometry, although more often for gaseous and highly volatile samples than for solids and liquids. In this project, we present a rapid and sensitive method for detecting mycotoxins and demonstrate its capability for the detection of aflatoxin B1, zearalenone, and ochratoxin A in food samples. Our method is based on thermal desorption coupled to dielectric barrier discharge ionization mass spectrometry (TD-DBDI-MS), which we show generates minimal interferences and produces almost exclusively molecular ions. We detected mycotoxins in various food samples, including corn, peanuts, millet, and rice. Our method has a linear dynamic range of 1 μg kg^{-1} to 100 μg kg^{-1} for all three mycotoxins and a limit of detection (LOD) of 0.31 μg kg^{-1}, 0.28 μg kg^{-1} and 0.43 μg kg^{-1}, respectively. It is simple, rapid, reduces the pretreatment steps and has significant potential for practical applications.

1 Introduction

Mycotoxins are a group of highly poisonous organic molecules that are secondary metabolites produced by several species of molds that grow on crops.[1–6] They can contaminate a range of grains in the field at the post-harvest stage and during food storage.[7] According to the exposure level, they exhibit immunotoxicity, liver toxicity, and teratogenic and carcinogenic effects.[8,9] Among various known mycotoxins, aflatoxin B1 is one of the most precarious and lethal.[10] To avoid adverse consumer health effects from dietary intake of these mycotoxins, maximum levels (MLs) of 75 μg kg^{-1} for zearalenone, 2 μg kg^{--1} for aflatoxin B1, and 3 μg kg^{-1} for ochratoxin A in cereals (cereals intended for direct human consumption) have been set by the European Commission (EC).

The commonly used methods for the detection of mycotoxins include gas chromatography (GC), thin layer chromatography, high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS), surface plasmon resonance, sensors, and enzyme-linked immunosorbent assays.[11–17] An enzyme-linked immunosorbent assay (ELISA) can be used for the rapid detection of mycotoxins, even in the field. However, the long preparation period and the poor reproducibility of antibodies severely hinder the application of ELISA.[18,19] GC, HPLC, and LC-MS/MS can achieve determination of mycotoxins with very high sensitivity and good accuracy, but their application in food monitoring is limited by the long times required to run chromatographic analyses.[17,18] Because of the complicated components present in agricultural products and the trace amounts of aflatoxins present, an efficient sample pretreatment, including sample clean-up and pre-concentration, is absolutely required for the protection of LC columns.[20] Furthermore, detection *via* HPLC or GC often requires derivatization.[21] Direct mass spectrometric detection instead of chromatography has the potential to greatly shorten the analysis time.

Since its inception, dielectric barrier discharge ionization (DBDI) has been an attractive ionization source due to its high efficiency and ability to operate at atmospheric pressure.[22] The DBDI ion source is highly sensitive and effective in detecting small organic molecules. It has been used to quickly distinguish between L-valine, L-proline, L-serine, and L-alanine when they are mixed together. The limit of detection for L-alanine is 3.5 picomoles using single-ion monitoring.[22] It is now widely applied[22–28] in biochemical analysis, environ-

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mental monitoring, food safety, forensic authentication, online monitoring of reaction intermediates, and mass spectrometry imaging (MSI), underscoring its universality. Here, we constructed a DBDI source in the "active sampling capillary" configuration.[29] In this method, desorption and ionization processes occur at different times and locations. Desorption takes place in a small oven, while ionization occurs in the DBDI source. The study focuses on quantification and reproducibility, and the results demonstrate the potential of this method for the fast detection of drugs and contaminants in complex samples.

2 Materials and methods

2.1 Materials

Ochratoxin A (purity 98%) was purchased from Shanghai Canspec Scientific Instruments Co. Zearalenone (purity 98%) was purchased from Shanghaixinbo Technology Co., Ltd, Shanghai, China. Aflatoxin B1 (purity 98%) was purchased from Xiamensenke Technology Co., Ltd, Xiamen, China. Acetonitrile (analytically pure) was purchased from Xilong Scientific Co. A corn reference sample containing very low amounts of mycotoxins (aflatoxin B1 0.01 μg kg^{-1}, zearalenone 0.05 μg kg^{-1}, ochratoxin A 0.03 μg kg^{-1}) was purchased from Meizheng Bio-Tech; In the following, we call this "corn-low". Further reference samples with higher mycotoxin concentrations, "corn-high" (aflatoxin B1 30 ± 3 μg kg^{-1}, zearalenone 34 ± 4 μg kg^{-1}, ochratoxin A 47 ± 5 μg kg^{-1}), peanut (aflatoxin B1 55 ± 4 μg kg^{-1}, zearalenone 12 ± 3 μg kg^{-1}, ochratoxin A 9 ± 3 μg kg^{-1}), millet (aflatoxin B1 63 ± 5 μg kg^{-1}, zearalenone 45 ± 4 μg kg^{-1}, ochratoxin A 44 ± 4 μg kg^{-1}), and rice (aflatoxin B1 32 ± 3 μg kg^{-1}, zearalenone 10 ± 3 μg kg^{-1}, ochratoxin A 58 ± 6 μg kg^{-1}) were also purchased from Meizheng Bio-Tech. The concentrations of these mycotoxins were certified by the supplier using HPLC. Finally, corn with unknown mycotoxin concentration was purchased from Xiamen Xinhuadu supermarket.

2.2 Methods

2.2.1 Solution preparation. Preparation of acetonitrile solution of mycotoxin: 1 mg aflatoxin B1, zearalenone and ochratoxin A were weighed in and dissolved in 10 ml acetonitrile respectively. From this, 100 mg L^{-1} stock solutions were prepared, and frozen at −20 °C. For use, we diluted the reserve solution with acetonitrile to obtain standard solutions of any desired concentration. The same steps were followed to prepare ethanol and methanol solutions of the mycotoxins. Units of μg L^{-1} represent mycotoxin concentrations in solution, whereas μg kg^{-1}, represent mycotoxin concentrations grains.

2.2.2 Corn-low pretreatment. The 20 g "corn-low" sample was ground into a fine powder using a mortar, for about 10 min. It was then divided into seven portions of 1 g each. Then, 10 μL of an acetonitrile solution of aflatoxin B1 were spiked into 1 g of the powder, using concentrations ranging from 100 μg L^{-1} to 10 000 μg L^{-1}. The mixture of corn powder and 1 ml acetonitrile was shaken for one minute using an oscillator, and then the mixture was extracted with an ultrasonic cleaning machine for 30 minutes. After this, the extracted corn-low powder and acetonitrile mixture was centrifuged for 1 minute, and the supernatant was filtered using a filter with a porosity of 0.45 μm. The acetonitrile solution of ochratoxin A and the acetonitrile solution of zearalenone were added in the same way as the above experimental steps.

2.2.3 Corn-high, peanut, rice and millet pretreatment. The pretreatment method of corn-high, rice, millet and peanut was the same as that of corn-low.

2.2.4 Pretreatment of corn from supermarket that was allowed to mold. The corn was soaked in deionized water for 12 hours. It was then placed in a beaker and left at a temperature of 25 °C for 5 days to become moldy. The moldy corn was dried at 50 °C and ground to a fine powder. The moldy corn was divided into seven portions of 1 g each. Using a microsyringe, 10 μL of aflatoxin B1 acetonitrile solution, zearalenone acetonitrile solution and ochratoxin A acetonitrile solution were added to each portion of the powdered reference samples. The concentration of the solutions ranged from 100 μg L^{-1} to 3000 μg L^{-1}. The powder was thoroughly mixed after each addition. 1 mL of acetonitrile was then added to each portion of moldy corn powder. Each set of samples was shaken for one minute, and then extracted ultrasonically for 30 minutes in an ultrasonic bath. After that, each portion of extracted samples was centrifuged for 1 minute, and the supernatant was filtered to obtain the filtrate for use.

2.2.5 Mass spectrometry and MS setup. A quadrupole time-of-flight (Q-TOF) mass spectrometer (API-TOF, TOFWERK AG., Thun, Switzerland) was used in this work. Typical instrumental settings were as follows: TOF extraction rate (repeller plate pulsing rate), 16 kHz; capillary voltage, 0 V; capillary temperature, 180 °C. Data acquisition was performed using a mass window of m/z 7–566 at a mass resolution of 5000 (full width at half-maximum at m/z 313). The air flow rate into the ionization source was 0.7–0.8 L min^{-1}. All experiments were performed in positive ion mode. The Tofware software version 3.2.1 (TOFWERK) was used for data post-processing, and OriginPro 2019 (OriginLab, Northampton, MA, U.S.A.) was used for preparing the figures containing mass spectra.

2.3 Ionization source and thermal desorption device

The device designed for sample introduction is shown in Fig. 1. Air, as carrier gas, entered the ion source chamber at a constant flow rate dictated by the MS inlet pumping rate. A miniature high-temperature ceramic heating plate was used for heating a 1.15 mm i.d. glass capillary. The sample is heated and desorbed after being delivered by the microsyringe into the glass capillary, then ionized inside the DBDI, and finally enters the mass spectrometer. The operating temperature was optimized as described below. The home-built DBDI source used in this experiment was designed according to previous research[23,25,30] and can be easily interfaced to any MS system having an atmospheric pressure interface. Compared

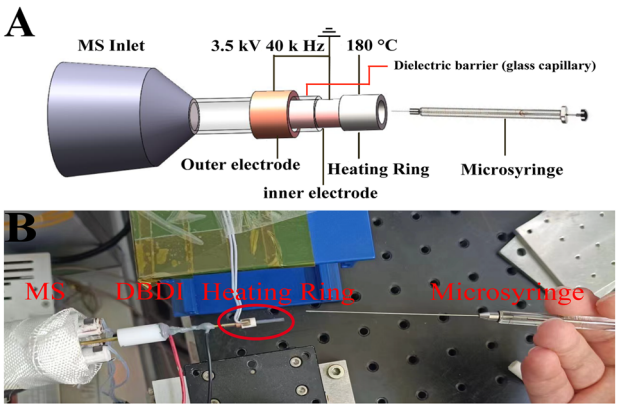

Fig. 1 (A) Schematic diagram of the TD-DBDI-MS setup, and (B) photograph of the actual device.

with other ambient ionization methods, the DBDI source directly ionizes the desorbed substances because they are forced to flow through the device, and the ionization efficiency is improved.[31] Because the desorption space is small and the space is constrained, the transfer efficiency of the desorption samples is also greatly improved[31] compared to open type DBDI.

3 Results and discussion

3.1 Selection of ion signals for quantitation

Fig. 2 displays the mass spectra of mycotoxins obtained by thermal desorption dielectric barrier discharge ionization mass spectrometry (TD-DBDI-MS). The ions generated by these three mycotoxins after being ionized are predominantly $[M + H]^+$. This is because the air was humid, and during the ionization process, water molecules and the three mycotoxin molecules undergo proton transfer reactions to produce $[M + H]^+$. This leads to a rather gentle ionization using DBDI. Because $[M + H]^+$ is the principal ion produced, it is used for quantitation in the subsequent experiments. The intensity (y scale) in all subsequent figures refers to the signal strength of $[M + H]^+$.

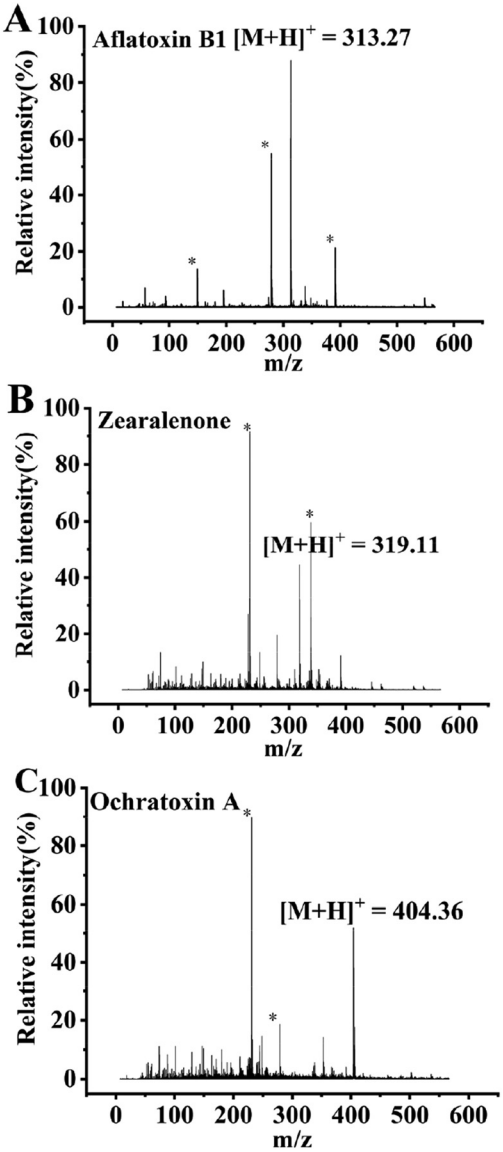

Fig. 2 (A) Mass spectrum of aflatoxin B1. (B) Mass spectrum of zearalenone. (C) Mass spectrum of ochratoxin A. Asterisks are peaks originating from plasticizers present in laboratory air.

3.2 Optimization of TD-DBDI-MS conditions

As seen in Fig. 3A, for the protonated aflatoxin B1, zearalenone, ochratoxin A, the signal intensity increases with increasing desorption temperature, leveling off at 180 °C. This may be due to the Leidenfrost phenomenon that the liquid cannot wet an overheated surface, leading to unstable desorption, so the signal intensity is unstable. Thus, a temperature of 180 °C was deemed sufficient for these compounds.

Evaluation of the injected volume is also important for such methods. Fig. 3B illustrates the relationship between the signal intensity and the sample volume delivered by the microsyringe, using a temperature of 180 °C. It was found that the signal intensity of the analytes became higher as the volume increased; however, when the volume reached 0.8 μL, the signal intensity started to plateau. When the desorption solution fills the desorption chamber, increasing the volume causes the analyzed substance to overflow and does not increase the rate at which the analyte enters the mass spectrum. Unless otherwise specified, the experimental conditions for the following experiments will be 180 °C and 0.8 μL for temperature and volume, respectively.

The choice of solvent and extraction time for mycotoxin extraction from grains is crucial. Fig. 3C illustrates the relationship between extraction time and signal strength of corn-high with different solvents. The graph shows that signal strength does not increase after the extraction time exceeds 30 minutes. The strongest TD-DBDI-MS signal was obtained after extraction of the corn-high sample with acetonitrile. Aflatoxin B1 in corn-high can be fully dissolved in 1 mL methanol, ethanol or

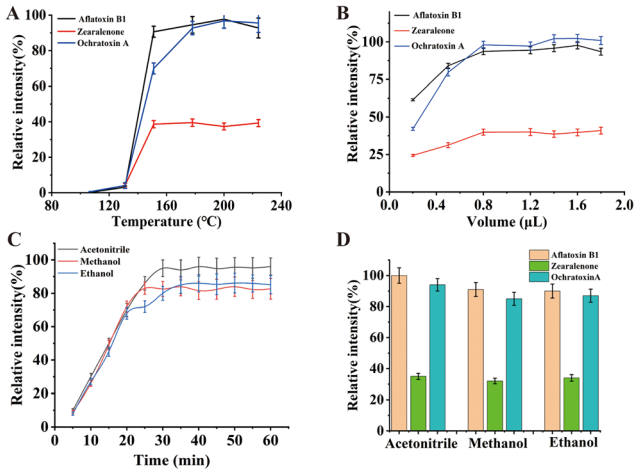

Fig. 3 (A) Effect of desorption temperature on signal strength. (B) Effect of single injection volume on signal strength. (C) Effect of extraction time on signal strength using "corn-high" as a sample. (D) Effect of different extraction solvents on signal strength using "corn-high" as a sample.

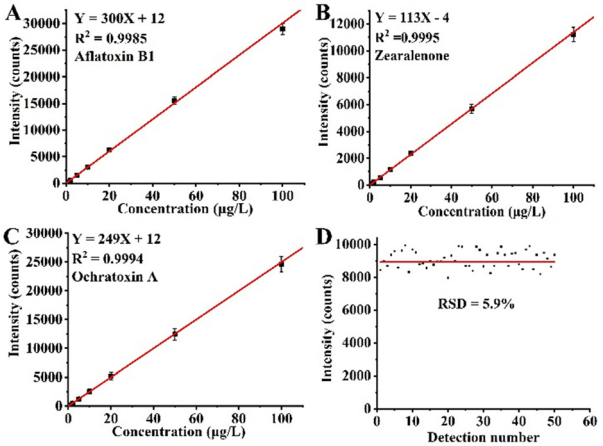

Fig. 4 (A–C) Calibration curves for aflatoxin B1, zearalenone and ochratoxin A, with the intensity of the $[M + H]^+$ peak plotted as a function of injected concentration. (D) Aflatoxin B1 was tested repeatedly, 50 times.

acetonitrile. Similarly, zearalenone and ochratoxin A were also evaluated for signal intensity of the protonated molecular ion peaks with methanol, ethanol and acetonitrile solutions (Fig. 3D). Apparently, the different solvents only affect the ionization efficiency in a minor way, presumably because they are evaporated; acetonitrile had a slight advantage. It was concluded that acetonitrile solutions of aflatoxin B1, zearalenone and ochratoxin A led to the highest ionization efficiency after desorption.

3.3 Quantification of mycotoxins in acetonitrile solution

To test the method's ability to quantify, the detection sensitivity, and the signal stability, we used acetonitrile solutions of three standards, aflatoxin B1, zearalenone, and ochratoxin A with concentrations of 1, 2, 5, 10, 20, 50 and 100 μg kg^{-1}. We then recorded calibration curves using our TD-DBDI-MS setup. Each concentration was measured 10 times, and the measured the peak signal intensity of protonated ions of aflatoxins B1, zearalenone, and ochratoxin A were plotted against the concentration of the acetonitrile solutions, as shown in Fig. 4A–C. We were able to establish a linear response over two orders of magnitude. Using a 3× signal-to-noise ratio (S/N = 3), we calculated their detection limits to be as low as 0.12 μg L^{-1}, 0.13 μg L^{-1} and 0.15 μg L^{-1}, respectively. Next, we prepared 50 samples containing a concentration of 30 μg L^{-1} aflatoxin B1 to test the method's signal stability. As shown in Fig. 4D, the abscissa represents the sampling times, the ordinate represents the mass spectrum signal intensity, and the red curve represents the mean value of the signal. It is easy to see that the signal stability of this method is good (RSD = 5.9%).

3.4 Limits of detection and accuracy of the method

First, we attempted to measure mycotoxins in the extract of corn-low using the standard addition method. We obtained a standard addition curve for the signal peak intensity of $[M + H]^+$ of the three mycotoxins and their concentrations added in corn-low, shown in Fig. 5. The added concentrations of all data points were normalized to 1 g corn-low as the total mass. The near-zero intercepts of the standard addition curves indicate that the concentrations of mycotoxins in these samples is very small. We determined the detection limits to be 0.31 μg L^{-1}

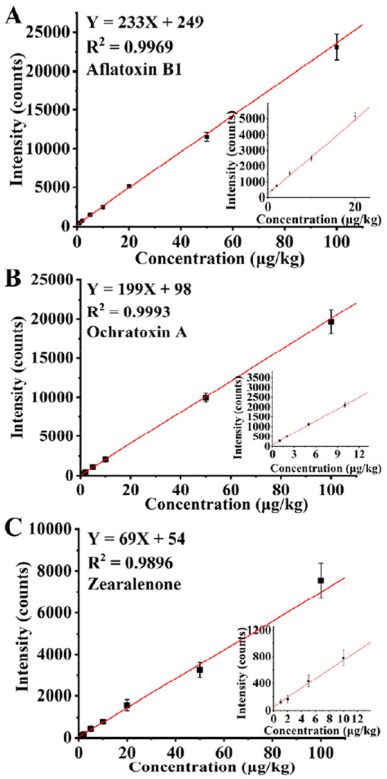

Fig. 5 Standard addition curves for corn-low. (A) aflatoxin B1, (B) ochratoxin A, (C) zearalenone.

(aflatoxin B1), 0.28 μg L^{-1} (zearalenone) and 0.43 μg L^{-1} (ochratoxin A), respectively, based on the S/N = 3 criterion, and a standard square variance (R^2) > 0.98. Moreover, LOD and linear dynamic range of the proposed method are comparable to those available for other analytical approaches. Unfortunately, we were unable to quantify these three mycotoxins in the corn-low sample, because they are present ≈1 order or magnitude below our limit of detection (Table 1).

To verify the accuracy of TD-DBDI-MS, we conducted a mass spectrometric analysis of the extracts of the reference samples with higher mycotoxin concentrations, by adding various amounts of mycotoxin standards. We found a good linear response for aflatoxin B1, zearalenone, and ochratoxin A in the four cereals between the signal intensity and the concentration of the mycotoxins added (Table 2). The correlation coefficient R^2 was greater than 0.98, and the recovery rate (measured mycotoxin concentration/actual mycotoxin concentration) ranged from 82% to 118%. These findings indicate that TD-DBDI-MS can quantitatively detect three types of mycotoxins in the four cereals.

3.5 Detection of mycotoxins in moldy corn

Finally, the method was used to detect mycotoxins in moldy corn. For this, standard addition plots (signal intensity *vs.* concentration of mycotoxin standard acetonitrile solution added) in extracts of moldy corn were established. Each data point was measured five times, and the standard curve is shown in Fig. 6, with the corresponding correlation coefficients R^2 being greater than 0.98.

Table 1 Comparison with other detection technique for aflatoxins

Method	LOD (μg kg^{-1})	Linearity (μg kg^{-1})	Ref.
Biosensor-based	0.97	1.67–17.8	32
LC-MS	10	10–600	33
HPLC fluorescence detector	3.5	4–20	34
TLC densitometric analysis	1.2–1.7	1–9	35
UV–vis enzymatic method	10	10–60	36
DBDI-MS	0.28	1–100	This work

The concentrations of aflatoxin B1, ochratoxin A and zearalenone determined were 45.2 μg kg^{-1}, 29.6 μg kg^{-1}, and 20.7 μg kg^{-1}, respectively. These values are above the legally tolerated limits for mycotoxins in foodstuffs. For example, in China, the content of aflatoxin B1, ochratoxin A and zearalenone in food should not exceed 20 μg kg^{-1}, 5 μg kg^{-1} and

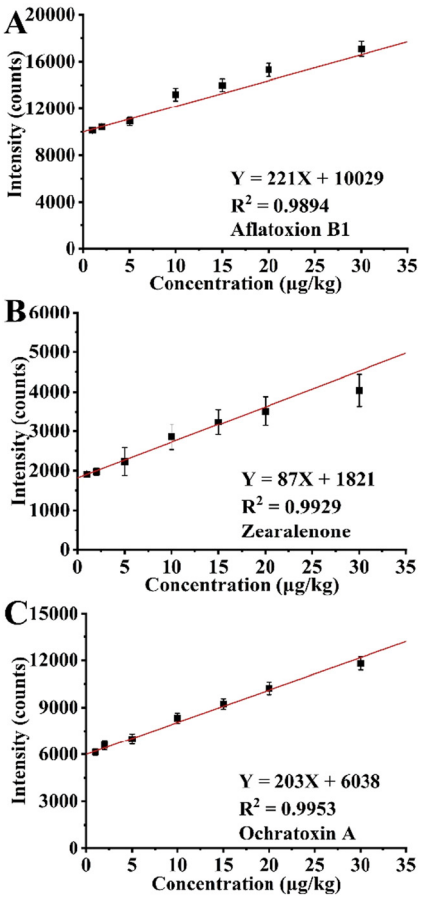

Fig. 6 Standard addition curve for moldy corn-high. (A) aflatoxin B1, (B) zearalenone, (C) ochratoxin A.

Table 2 Detailed data on mycotoxins in corn-high, millet, peanut and rice standard materials

Analyte	Certified mycotoxin contentration present (μg kg^{-1})	Linear relationship of standard addition measurement	Correlation coefficient (R^2)	Measured mycotoxin concentration (μg kg^{-1})	LOD (μg kg^{-1})	Repeatability (RSD, %, n = 10)	Recovery (mean ± SD, in %, n = 5)
Aflatoxin B1 in corn-high	30 ± 3	$Y = 256x + 781$	0.9946	27 ± 3	0.252	8.6	90 ± 10
Aflatoxin B1 in millet	63 ± 5	$Y = 258x + 1647$	0.9901	58 ± 5	0.263	6.7	92 ± 8
Aflatoxin B1 in peanut	55 ± 4	$Y = 207x + 1156$	0.9955	54 ± 4	0.324	8.4	98 ± 8
Aflatoxin B1 in rice	32 ± 3	$Y = 137x + 450$	0.9946	38 ± 4	0.258	9.3	118 ± 12
Zearalenone in corn-high	34 ± 4	$Y = 75x + 257$	0.9783	29 ± 2	0.169	8.1	85 ± 6
Zearalenone in millet	45 ± 4	$Y = 62x + 280$	0.9925	39 ± 5	0.316	6.5	87 ± 10
Zearalenone in peanut	12 ± 3	$Y = 81x + 99$	0.9966	9 ± 2	0.197	9.6	76 ± 14
Zearalenone in rice	10 ± 3	$Y = 104x + 101$	0.9926	11 ± 1	0.265	4.6	110 ± 7
Ochratoxin A in corn-high	47 ± 5	$Y = 205x + 971$	0.9951	49 ± 5	0.218	9.5	105 ± 11
Ochratoxin A in millet	44 ± 4	$Y = 303x + 2030$	0.9998	46 ± 3	0.426	7.6	105 ± 8
Ochratoxina in peanut	9 ± 3	$Y = 169x + 992$	0.9961	7 ± 1	0.195	6.8	82 ± 9
Ochratoxin A in rice	58 ± 6	$Y = 169x + 992$	0.9961	48 ± 4	0.319	7.3	82 ± 7

60 μg kg^{-1}, respectively. In Europe, the content of aflatoxin B1, ochratoxin A and zearalenone in food should not exceed 2 μg kg^{-1}, 20 μg kg^{-1} and 2 μg kg^{-1}.

4 Conclusions

In this study, thermal desorption coupled to a dielectric barrier discharge ionization source and a mass spectrometer was used to quantitatively detect aflatoxin B1, ochratoxin A and zearalenone in corn, rice, millet and peanut samples. The LODs of aflatoxin B1, ochratoxin A and zearalenone were as low as 0.31 μg L^{-1}, 0.28 μg L^{-1} and 0.43 μg L^{-1} respectively. In addition, this method shortens the detection time of mycotoxins in a sample to about 2 min (excluding the extraction step) and is accurate; the recoveries were between 76% and 118%. This method can be used for rapid detection and screening of mycotoxins in cereals. The results indicate that thermal desorption DBDI mass spectrometry is a simple and rapid analytical tool for quantification of these mycotoxins in commercial foods.

Author contributions

Xiangxu Zhao: conceptualization, methodology, formal analysis, investigation, data curation, and writing – original draft. Xiaokang Guan: investigation, methodology, validation, and formal analysis. Qiao Lu: investigation, methodology, data curation, and formal analysis. Xiaowen Yan: supervision, methodology, resources and writing – review & editing. Renato Zenobi: supervision, conceptualization, methodology, validation, resources, funding acquisition, and writing – review & editing.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

There are no conflicts to declare.

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