Application Progress of Time-of-Flight Mass Spectrometry in Screening Hazardous Factors in Agricultural Products

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Abstract Time-of-flight mass spectrometry (TOF-MS) is an advanced mass spectrometric technique characterized by a wide mass range, high resolution and mass accuracy, high sensitivity, and rapid analysis speed. It has been widely applied as a high-end detection tool in the field of rapid screening for hazardous factors in agricultural products. This review summarizes the principles, classification, and characteristics of time-of-flight mass spectrometry (TOF-MS), as well as its research progress in six application areas: agricultural product additives, contaminants, illegal additives, pesticide residues, veterinary drug residues, and mycotoxins. The future prospects of this technology are also discussed.

Key words Time-of-flight mass spectrometry (TOF-MS); Agricultural product; Hazardous factor; Screening; Application

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Contaminants and residues in agricultural products generated during production and processing or originating from packaging materials, such as pesticide residues, veterinary drug residues, illegal additives, and organic pollutants, pose a serious threat to the quality and safety of agricultural products. The complexity of agricultural product matrices and the diversity of contaminant types also place higher demands on detection technologies for agricultural products.

High-resolution time-of-flight mass spectrometry (TOF-MS) is characterized by a wide mass range, high resolution and mass accuracy, and fast analysis speed[1]. Unlike low-resolution mass spectrometry, TOF-MS can obtain accurate mass values and possible molecular formulas of compounds through full-scan acquisition, significantly enhancing its anti-interference capability in complex backgrounds and making the detection results more accurate and reliable. Moreover, TOF-MS offers a high scan rate, with theoretically no upper limit to the number of target compounds that can be simultaneously analyzed, enabling high-throughput detection of hundreds of pesticides in a single run indeedly. TOF-MS can also be used to establish a database of specific compounds. Automatic searching and confirmation can be performed using software by integrating information such as accurate mass values, retention time, and isotopic ratios obtained from sample analysis, enabling rapid identification of target compounds without the need for reference standards[2-3]. Therefore, TOF-MS serves as an effective tool for the qualitative analysis of trace compounds in complex samples, meeting the demands of high-throughput rapid screening and quantitative analysis.

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Classification of TOF-MS

Both mass spectrometry and chromatography offer distinct advantages, and integrating them into a single analytical system provides an optimal analytical approach. TOF-MS can be classified according to the type of chromatography or spectroscopy with which it is coupled, including liquid chromatography-time-of-flight mass spectrometry (LC-TOF-MS), gas chromatography-time-of-flight mass spectrometry (GC-TOF-MS), comprehensive two-dimensional gas chromatography-time-of-flight mass spectrometry (GC × GC-TOF-MS), and inductively coupled plasma orthogonal acceleration time-of-flight mass spectrometry (ICP-oa-TOF-MS)[7]. The coupling of LC and MS relies critically on interface technology. Based on the interface and ionization techniques, TOF-MS can be mainly categorized into ESI-TOF-MS combining electrospray ionization (ESI) with TOF-MS, APCI-TOF-MS combining atmospheric pressure chemical ionization (APCI) with TOF-MS, APPI-TOF-MS combining atmospheric pressure photoionization (APPI) with TOF-MS, and MALDI-TOF-MS combining matrix-assisted laser desorption/ionization (MALDI) with TOF-MS. Tandem mass spectrometry, which enables multi-stage mass spectrometric analysis, emerged as a mass spectrometry technology in the late 1970s. Based on the type of tandem mass spectrometry, TOF-MS can be classified into Q-TOF-MS consisting of quadrupole MS and TOF-MS, and IT-TOF-MS consisting of ion trap MS and TOF-MS.

Performance Characteristics of TOF-MS

Wide mass range

In theory, TOF-MS has no upper limit for mass analysis. However, in practice, its analyzable mass range is constrained by factors such as the slower flight velocity of high-mass ions, insufficient detector response to these ions, and limitations in data storage memory. Nevertheless, it can still achieve a mass range of up to 300 000 Da, far exceeding that of quadrupole and ion trap mass

spectrometers.

Fast analysis speed

As a pulsed mass analyzer, TOF-MS offers an exceptionally fast data acquisition rate, reaching up to 4 G/s. Emerging in recent years, ultra-high-performance liquid chromatography (UPLC), when coupled with TOF, has significantly shortened analyte retention times and reduced chromatographic peak widths, thereby further enhancing the speed of sample analysis.

High resolution

TOF-MS is classified as a high-resolution mass spectrometer, achieving resolution of up to 55 000. It enables the measurement of molecular masses to the fourth decimal place, allowing direct elemental composition analysis and molecular formula calculation. In contrast, quadrupole and ion trap mass spectrometers are low-resolution instruments capable of measuring only integer molecular masses and are unable to perform elemental composition analysis.

High mass accuracy

The mass accuracy of ions detected by TOF-MS in full-scan mode is over 100 times higher than that of conventional mass spectrometers, with precision reaching 5 ppm or even lower in accurate mass measurements. In contrast, quadrupole mass spectrometers, limited by instrumental precision, can only resolve masses to the nearest half-mass unit.

High sensitivity

The detector of TOF-MS is capable of simultaneously detecting ions across the entire mass range, and the use of quadrupole focusing ensures maximum ion transmission efficiency, significantly enhancing its sensitivity. While its sensitivity in selected ion monitoring mode is lower than that of quadrupole mass spectrometers, it is substantially higher in full mass scan mode.

Application of TOF-MS in Screening Hazardous Factors in Agricultural Products

Agricultural product additives

Agricultural product additives are various compounds permitted for use in agricultural products to improve their quality. Their usage levels in China must strictly comply with the provisions of GB 2760-2014, *National Food Safety Standard*: *Standard for the Use of Agricultural Product Additives*. However, the misuse of agricultural product additives remains one of the significant factors affecting the quality and safety of agricultural products. Therefore, rapid screening and confirmation of the presence of misused additives in agricultural products are particularly important. Chen[3] developed an LC-TOF-MS-based screening method for screening various illegally added and easily misused colorants in agricultural products, and constructed a corresponding screening database. Zhao *et al.* [8] established an HPLC-Q/TOF-MS method for screening 29 illegally added and restricted synthetic colorants in cheese, which demonstrated advantages such as a wide screening range and good applicability to agricultural products containing matrices such as proteins and fats. For agricultural product additives commonly used as specified in GB 2760-2014, LC or GC can already meet the routine detection requirements for monitoring their compliance. However, when detecting or screening a specific class of agricultural product additives, MS techniques such as TOF-MS offer advantages including rapid analysis, broad screening coverage, and high sensitivity.

Agricultural product contaminants

Wang *et al.* [9] developed an LC-IT-TOF-MS method for the simultaneous determination of 14 heterocyclic amine residues in meat products, and further established a method for the analysis of 14 heterocyclic amines in wine accordingly. Both methods feature short analysis time, enabling rapid screening of heterocyclic amines during the safety inspection of agricultural products. Dasgupta *et al.* [10] developed a GC × GC-TOF-MS method for the determination of 12 polychlorinated biphenyls, 12 polycyclic aromatic hydrocarbons, and bisphenol A, which are persistent environmental pollutants in grapes and wine. The method achieves excellent separation of the target analytes, reducing the likelihood of false-negative results at low residue concentrations. During the refining process of edible oils and fats, organic contaminants such as 3-chloro-1, 2-propanediol esters and glycidyl esters may be formed. These two contaminants are typically detected using indirect methods, which are prone to yielding inconsistent results. However, the LC-TOF-MS method established by Haines *et al.* [11] enables the direct detection of 3-chloro-1,2-propanediol esters and glycidyl esters in edible oils and fats. Its high resolution significantly reduces interference from impurities, thereby enhancing the sensitivity for detecting contaminants in edible oils and fats. Ha *et al.* [12] developed a GC × GC-TOF-MS method for the determination of two trans-octadecenoic acids (18 ∶ 1 trans-11 and 18 ∶ 1 trans-9) in meat products and partially hydrogenated edible oils. The method achieves complete separation of the chromatographic peaks of these two trans fatty acids, allowing the calculation of their ratio to identify the source of the trans fatty acids.

Illegal additives

Lu *et al.* [13] established a database of 36 illegally added drugs with weight-loss, lipid-lowering, and laxative effects in health products using UPLC-IT-TOF-MS. They developed a rapid screening and confirmation method, which shortens the time required to identify target compounds in the safety inspection of health products and improves detection efficiency. Hao *et al.* [14] detected the illegal additive rhodamine B in poultry meat by IT-TOF-MS and performed multi-stage mass spectrometric analysis on it. Chen *et al.* [15] established an analytical method for 13 illegal additives in agricultural products using GC × GC-TOF-MS. By employing GC × GC, 32 compounds were rapidly and effectively separated within 20.5 min, overcoming the technical difficulty that one-dimensional GC could not separate 9 of these compounds from matrix-interfering components, and reducing the method's detection limit by more than 10 times. Calbiani *et al.* [16] established a Micro LC-Q-TOF-MS method for the accurate detection of four Sudan dyes potentially added to red pepper products. Rebane *et al.* [17] reviewed various detection methods for Sudan dyes in

food products and compared the limits of detection of different approaches including Micro LC-ESI-Q-TOF-MS. They concluded that TOF-MS techniques offer higher sensitivity and resolution. In addition, Soltzberg *et al.* [18] adopted MALDI-TOF-MS to identify various types of pigments and dyes, while Djelal *et al.* [19] applied TOF-MS technology to analyze oxidative intermediates of illegally added dyes in agricultural products.

Pesticide residues

During crop cultivation, relevant pesticides may be scientifically applied to reduce pests and diseases. However, due to the lack of strict management of pesticide use in China, there have been instances of using prohibited pesticides or misusing pesticides. This results in excessive pesticide residues in primary agricultural products or prepackaged agricultural products made from them, posing a potential threat to food safety. Jiang *et al.* [20] developed a GC × GC-TOF-MS method for the determination of 64 pesticide residues in vegetables. Using this method to analyze market samples, they detected residues of acephate and cypermethrin in two samples, with measured values of 0.036 and 0.107 mg/kg, respectively. Zhao *et al.* [21] established a rapid screening method for 281 pesticide residues in apples, tomatoes, and cabbages using QuEChERS combined with LC-Q-TOF/MS. The limits of detection for the method were 0.03 – 4.47 μg/kg, 0.01 – 4.49 μg/kg, and 0.02 – 3.61 μg/kg, respectively. Lacina *et al.* [22] developed a screening method for 212 pesticide residues in plant-derived agricultural products using ultra-high-performance liquid chromatography coupled with time-of-flight mass spectrometry (UPLC-TOF-MS) combined with QuEChERS pretreatment. At a resolution of 10 000 FWHM, UPLC-TOF-MS detected over 96% of the target pesticides in the samples. Ferrer *et al.* [23] analyzed 101 pesticides using LC-TOF-MS with a mass window width set to 0.05 Da. They obtained accurate mass values for the 101 pesticides in green pepper and conducted accurate screening and confirmation.

Veterinary drug residues

Zhang *et al.* [24] developed an analytical method for 19 antibiotics in dairy products using UPLC-Q-TOF-MS combined with a database. The retention time deviation was less than 0.1 min. The mass deviation was less than 5 mDa, and the isotopic pattern matching score was no less than 87.4%. Meng *et al.* [25] developed a rapid screening method for eight fluoroquinolones, five sulfonamides, and their four acetylated metabolites in dairy products using UPLC-Q-TOF-MS. The limits of quantification ranged from 0.5 to 0.8 μg/kg for fluoroquinolones, and from 0.5 to 13.0 μg/kg for sulfonamides and their metabolites. The relative standard deviations of the average recoveries were all less than 15%. Paschoal *et al.* [26] also developed an analytical method for the determination of six quinolone drugs, namely, flumequine, oxolinic acid, sarafloxacin, danofloxacin, enrofloxacin, and ciprofloxacin in tilapia, using LC-ESI-Q-TOF-MS. Hermo *et al.* [27] compared the detection sensitivity of LC-TOF-MS, LC-MS, and LC-MS/MS for seven quinolone drugs in pig liver. The results showed that the limits of quantification ranged from 0.5 to 1.0 μg/kg for the LC-MS/MS method, from 1.5 to 6.0 μg/kg for the LC-TOF-MS method, and from 2.0 to 6.0 μg/kg for the LC-MS method.

Mycotoxins

Zhang *et al.* [28] established an LC-IT-TOF-MS screening method for 10 mycotoxins (aflatoxin B_1, aflatoxin B_2, aflatoxin G_2, aflatoxin G_2, α-zearalenol, β-zearalenol, zearalanone, and zearalenone) in distillers dried grains with solubles from corn. Through accurate mass matching and retrieval of the standard spectral library of characteristic secondary fragment ions, simultaneous qualitative screening and quantitative analysis of different mycotoxin compounds can be achieved. Sirhan *et al.* [29] established an LC-ESI-Q-TOF-MS method for the detection of four aflatoxins in five agricultural products susceptible to aflatoxin contamination, *i. e.*, barley, wheat, corn, peanuts, and peanut butter, with a limit of quantification of 0.8 μg/kg. Luo *et al.* [30] applied TOF-MS to elucidate the degradation product structures and toxicity of aflatoxin B_1 in ozonated water.

Prospects

As a mass spectrometric detector characterized by high resolution, accuracy, and sensitivity, TOF-MS demonstrates outstanding technical advantages in trace analysis of contaminants in agricultural products. It is foreseeable that in the field of food safety research, TOF-MS will become a research and application hotspot in areas such as high-throughput and high-sensitivity rapid screening and confirmatory analysis of known multi-component trace compounds, separation and analysis of complex systems, as well as screening and analysis of unknown compounds and metabolites.

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