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Development of brush ionization probe mass spectrometry for convenient on-site detection of traditional Chinese medicine

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Abstract

Objective: To develop a convenient, direct, and highly sensitive method for screening trace chemical additives in complex Chinese patent medicines, thereby addressing core technological bottlenecks in pharmaceutical analysis and quality control.

Methods: A brush ionization probe device was independently designed and constructed, and an efficient detection method was established through systematic optimization of key parameters. Twenty-three Chinese patent medicine samples, representing 6 dosage forms (capsules, tablets, pills, granules, powders, and liquid preparations), were analyzed using 10 common chemical additives as target analytes.

Results: All samples were successfully analyzed without complex pretreatment, and 5 chemical additives were detected in 7 Chinese patent medicines. The brush ionization probe device exhibited cost-effectiveness (~0.2 USD per probe), operational simplicity, rapid analysis (~10 s per sample), high efficiency, and minimal reagent consumption (~10 μL per sample).

Conclusion: This advancement is expected to provide an innovative scientific tool for improving the generality and convenience of on-site quality control, while promoting technological progress in disciplines such as pharmacology and traditional Chinese medicine.

Key words: Ambient mass spectrometry; Brush ionization probe; Chinese patent medicines; Quality control; Rapid detection

1. Introduction

Chinese patent medicines (CPMs) are a category of traditional Chinese medicine (TCM) products prepared from Chinese medicinal materials as raw ingredients and used to prevent and treat diseases according to prescribed formulas.[1,2] As an indispensable component of TCM, CPMs have a long history, offer remarkable therapeutic effects, and are convenient to carry and store. They are produced in diverse dosage forms, including pills, tablets, powders, granules, and injections, with correspondingly complex prescriptions and manufacturing processes.[3] In recent years, some manufacturers have added chemical drug components to CPMs to address limitations such as slow onset of action, prolonged treatment courses, and high dosages, seeking synergistic effects with TCM ingredients.[4] Moreover, there are still manufacturers who illegally incorporate fast-acting chemical additives into CPMs without proper registration or prescription labeling, aiming to enhance short-term efficacy and gain substantial profits.[5] Such adulteration not only poses serious threats to public health and safety but also disrupts market order. Therefore, establishing a sensitive, accurate, and efficient screening method for chemical additives is urgently needed and holds great significance for producers, consumers, and regulators.

With the advancement of modern analytical technology and the continuous improvement of quality control systems for CPMs, rapid inspection methods have also developed rapidly. Currently, many effective techniques are available for detecting chemical additives in CPMs,[6] including vibration spectroscopy methods such as Raman spectroscopy,[7] mid-infrared spectroscopy (MIR),[8] and near-infrared spectroscopy (NIR)[9]; chromatographic techniques such as thin-layer chromatography and high-performance liquid chromatography (HPLC)[10,11]; and chromatographic-mass spectrometry (MS) methods such as liquid chromatography–mass spectrometry (LC-MS) and gas chromatography–mass spectrometry (GC-MS).[12,13] However, these methods have notable limitations in specificity, accuracy, sensitivity, and universality, and they are often associated with

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long analysis time and high costs.[14] Moreover, during complex sample pretreatment procedures, target analytes are prone to loss or degradation. Following the development of desorption electrospray ionization (DESI) technology by Professor Cooks at Purdue University,[15] a new class of ionization techniques collectively known as ambient MS has gradually emerged. Successive methods such as oEESI-MS,[16] PnESI-MS,[17] and UEN/CFI-MS have been developed,[18] which enable ionization of sample molecules under ambient pressure, show strong resistance to matrix interference, eliminate the need for pretreatment, and allow rapid analysis. Nevertheless, these technologies still face challenges with complex sampling and sample-loading processes. They struggle to achieve universality, handheld convenience, and direct rapid analysis of samples with complex morphologies. Therefore, more convenient and efficient analytical strategies for the rapid and sensitive screening of chemical additives in complex CPMs are urgently needed.

Herein, a brush ionization probe mass spectrometry (BIP-MS) device was developed for screening chemical additives in CPMs across various dosage forms. The method features notable advantages, including a simple device structure, convenient operation, strong universality, rapid analysis (~10 s per sample), and cost-effectiveness (~0.2 USD per probe). Twenty-three CPMs representing 6 dosage forms, such as capsules, tablets, pills, granules, powders, and liquid preparations, were analyzed using 10 common chemical additives as target analytes. All samples were rapidly and directly characterized without complex pretreatment. Analysis of the complex MS fingerprints of each CPM enabled the sensitive detection of prescription-listed chemical additives, including paracetamol, caffeine, chlorpheniramine maleate, glibenclamide, and clonidine, across different dosage forms, demonstrating the excellent generalizability and sensitivity of BIP-MS. Overall, this BIP-MS-based strategy for the rapid quality assessment of complex CPMs holds promise for advancing pharmaceutical analysis technologies and enhancing quality control.

2. Materials and methods

2.1. Samples, chemicals, and reagents

A total of 23 complex formulations were randomly collected from the market, representing 6 dosage forms: pills, tablets, powders, granules, capsules, and oral liquids. Detailed information is provided in Supplemental Table S1, https://links.lww.com/STCM/A70. Ten chemical additives commonly used by CPM manufacturers to enhance therapeutic efficacy were chosen as target analytes, including 3 anticold agents, 4 hypoglycemic agents, and 3 antihypertensive agents. These chemicals were purchased from Beijing Beiterenkang Biotechnology Co., Ltd. (Beijing, China). All standards had a purity of >98%. Methanol (HPLC grade) and formic acid (HPLC grade) were obtained from Merck (Darmstadt, Germany), and ultrapure water was supplied by Watsons (Hong Kong, China).

All standard samples were prepared as 1.000 mg/mL stock solutions in methanol, except for phenformin, which was dissolved in ultrapure water. The stock solutions were serially diluted to final concentrations of 5, 10, 50, 100, 250, 500, and 1000 ng/mL. All solutions were stored at −20 °C and protected from light.

2.2. BIP-MS device construction

A BIP, coupled with a linear ion trap quadrupole (LTQ XL) mass spectrometer (Thermo Scientific, San Jose, California, USA), was developed for the convenient and rapid analysis of complex, multimorphological CPMs. As shown in Figure 1, the main components of the BIP comprise 3 parts: a wooden handle, an inert metal ring, and polyamide fiber bundles. The wooden handle enables handheld sampling and provides insulation; the inert metal ring connects the other 2 parts and, due to its conductivity, allows the application of high voltage; and the polyamide fiber bundle forms the probe tip, rapidly adsorbing and storing both solvents and analytes. Before use, the probe was soaked and ultrasonically cleaned with solvents such as deionized water, methanol, and dichloromethane.

2.3. Key parameter optimization of BIP-MS

To achieve optimal MS response and detection sensitivity, key MS conditions were systematically optimized, including extraction solvents, spray voltage, and collision-induced dissociation (CID) energy. Five extraction solvents were compared: methanol, 75% methanol, 50% methanol, 25% methanol, and water. Spray voltage is critical for ionization efficiency: insufficient voltage leads to low analyte ionization, whereas excessively high voltage can cause arcing at the probe tip and signal instability. Spray voltage was therefore optimized within the range of 2.0 to 5.0 kV using appropriately diluted antihypertensive drug standard solutions. The capillary temperature was set at 275 °C, and other MS tuning parameters (capillary voltage 35 V, tube lens voltage 140 V) were automatically optimized by the instrument. To obtain high-quality MS/MS data for accurate compound identification, the optimal CID energy for each compound was determined using standard solutions. The optimal energy was selected when the intensity of the parent ion peaks in the MS/MS spectra accounted for approximately 10%–30% of the base peak.

2.4. Evaluation of qualitative and quantitative performance of BIP-MS device

Under the optimized analytical conditions, BIP-MS was used to analyze mixed standard solutions across a range of concentrations, and calibration curves were generated via linear fitting.

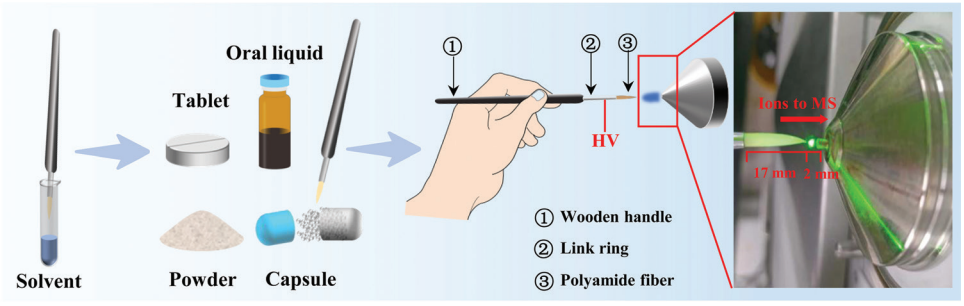

Figure 1. Architecture of the BIP-MS and its analysis workflow.

Precision was evaluated by six replicate analyses of the standard solution, with the relative standard deviation (RSD) as the evaluation index. The limit of detection (LOD) and limit of quantitation (LOQ) were defined as the concentrations corresponding to signal-to-noise ratios (S/N) of 3 and 10, respectively. Using the CPM Jiangtang Tongmai Capsules, which contain no chemical additives, as the blank matrix, caffeine, pioglitazone, and clonidine were selected as representative chemical additives commonly found in anticold, hypoglycemic, and antihypertensive CPMs, respectively. The standard addition method was used to evaluate matrix interference, with the matrix factor calculated as follows: matrix factor = (A/B) × 100% (n = 3), where A is the mean signal intensity of the spiked matrix, and B is the mean signal intensity of the pure standard solution. Because no pretreatment was performed, the matrix effect results also reflect the recovery of the method.

2.5. Rapid analysis process for chemical additives in CPMs

Distinct sampling methodologies are required for different CPM dosage forms. For solid samples (such as capsules, pills, and tablets), the coating or shell is removed to expose the contents, which are then directly swabbed with a solvent-moistened probe. For liquid formulations (such as oral liquids), the solvent-moistened probe is directly immersed in the trace sample to adsorb the target analytes. After sampling, the probe tip is positioned approximately 2 mm from the ion transfer tube inlet. When the optimized voltage is applied, the solution on the probe tip undergoes electrospray ionization, forming a stable Taylor cone,[19] thereby completing the analytical procedure with high ionization efficiency.

3. Results and discussion

3.1. Development of novel BIP-MS device

A BIP-MS device featuring simplicity, ease of operation, strong universality, and stability was developed (Fig. 1). The core component is a polyamide fiber bundle composed of neatly arranged nylon 66 fibers of varying lengths. These soft, absorbent fibers function as a natural sample reservoir. Considering sample load and spray duration, a brush probe with a length of 17.0 mm and a diameter of 2.9 mm was selected, providing a spray time of up to 5 minutes and yielding stable, prolonged ion signals essential for high-quality MS data. Serving as both the sample pool and ionization medium, the brush probe integrates extraction and detection processes, significantly improving detection efficiency. Compared with other electrospray ionization methods (eg, toothpicks, paper, carbon fiber),[20–22] the brush probe offers lower cost, larger surface area, and superior solvent absorption, enabling continuous MS signals and efficient adsorption and extraction of target analytes (Supplemental Table S2, https://links.lww.com/STCM/A70). Relative to classical nano-ESI,[23] BIP-MS demonstrates higher sampling efficiency and signal continuity, mitigating capillary blockage and signal instability commonly associated with nano-ESI-MS, and is particularly suited for analyzing CPMs of various dosage forms with complex morphologies. The BIP-MS device is cost-effective (~0.2 USD per probe), operationally simple, rapid (~10 s per sample), highly efficient, and requires minimal reagents (~10 µL per sample).

3.2. Optimization of BIP-MS device parameters

To enhance detection performance and achieve accurate results, MS conditions were systematically optimized. Spray solvents can significantly affect sample dissolution and ionization efficiency. Methanol and its aqueous mixtures at varying ratios were tested as extraction and spray solvents (Fig. 2A–2C). In the cold medicine group, the ion signal intensities of caffeine, paracetamol, and chlorpheniramine maleate initially increased with rising methanol content. The signals of caffeine and paracetamol peaked at 25% methanol, and then declined, whereas chlorpheniramine maleate reached its maximum at 75% methanol, a level approximately three times higher than the peak

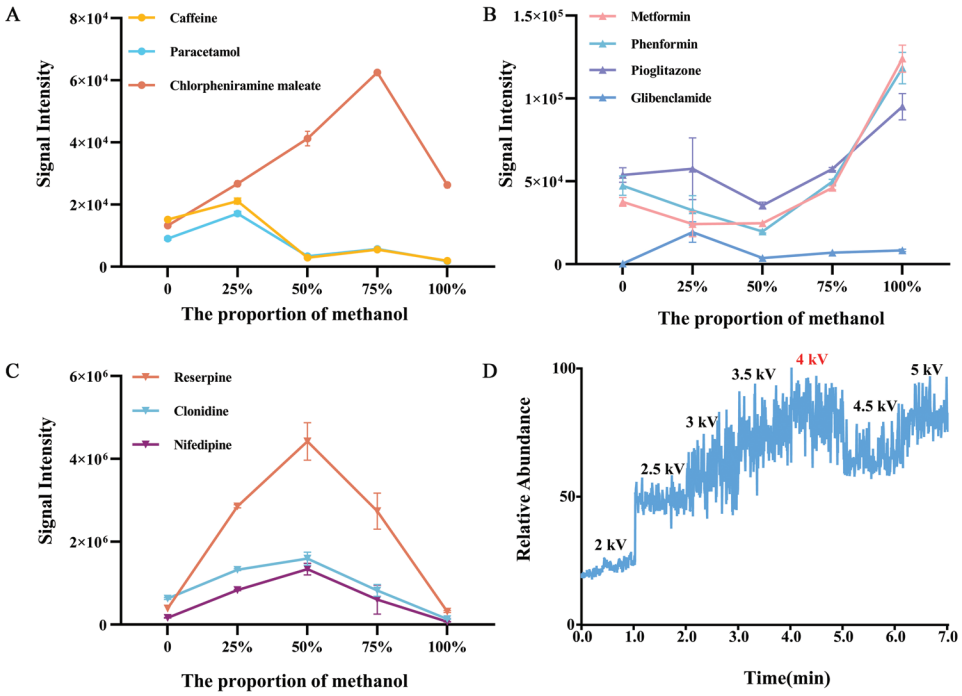

Figure 2. Effects of spray solvents on the signal intensities of chemical additives in (A) anticold CPMs, (B) hypoglycemic CPMs, and (C) antihypertensive CPMs. (D) total ion current (TIC) spectrum of antihypertensive CPMs for optimization of ionization voltage. Error bars represent the standard deviation of 3 replicate measurements.

signals of caffeine and paracetamol. Considering all 3 compounds, 25% methanol was selected as the optimal extraction and spray solvent. In the hypoglycemic drug group, although the signals of metformin, phenformin, and pioglitazone peaked at 100% methanol, glibenclamide exhibited extremely low signal under this condition. To improve applicability for quality control of hypoglycemic drugs, 25% methanol was selected as the extraction and spray solvent. Ionization voltage was varied from 2.0 to 5.0 kV. Signal intensity increased between 2.0 and 4.0 kV, decreased sharply from 4.0 to 4.5 kV, and partially recovered between 4.5 and 5.0 kV, but remained below the 4.0 kV level. Therefore, 4.0 kV was selected as the optimal voltage for subsequent analyses (Fig. 2D). Through systematic optimization of spray solvent and ionization voltage, the optimal MS conditions for analyzing the target compounds were established, providing a solid foundation for subsequent detection.

3.3. Analytical performance evaluation of BIP-MS

The qualitative performance of BIP-MS was first evaluated by its ability to accurately capture molecular ion peaks and secondary CID fragments for all target analytes. The full-scan MS and MS/MS spectra of chemical additives commonly present in anticold, hypoglycemic, and antihypertensive CPMs are shown in Supplemental Fig. S1, https://links.lww.com/STCM/A70. Distinct MS signal peaks were clearly observed for all analytes, and the quasi-molecular ions, main fragment peaks, and acquisition parameters are summarized in Supplemental Table S3, https://links.lww.com/STCM/A70. In Supplemental Fig. S1A, https://links.lww.com/STCM/A70, the molecular ions of paracetamol, caffeine, and chlorpheniramine maleate were detected at *m/z* 152, 195, and 275, respectively (with *m/z* 230 as the in-source fragment ion of chlorpheniramine maleate). Supplemental Figure S1B–S1D, https://links.lww.com/STCM/A70, presents the MS/MS spectra and fragmentation patterns of caffeine (*m/z* 138, 110),[24,25] paracetamol (*m/z* 110),[26] and chlorpheniramine maleate (*m/z* 230) at the optimal CID energy.[27] Figure S1E, https://links.lww.com/STCM/A70, displays the full-scan spectrum of 4 chemicals commonly added to hypoglycemic CPMs: metformin (*m/z* 130, $[M+H]^+$), phenformin (*m/z* 206, $[M+H]^+$), pioglitazone (*m/z* 357, $[M+H]^+$), and glibenclamide (*m/z* 494, $[M+H]^+$). In biguanides, C–N bond cleavage is typically favored. However, at 400 eV collision energy, the parent ion of metformin remained stable without fragment ions, allowing direct identification based on *m/z* 130 and its characteristic resistance to fragmentation (Supplemental Fig. S1F, https://links.lww.com/STCM/A70). Phenformin generated ions at *m/z* 189, 164, 105, and 60 (Fig. S1G, https://links.lww.com/STCM/A70), pioglitazone produced characteristic ions at *m/z* 134 and 119 (Fig. S1H, https://links.lww.com/STCM/A70), and glibenclamide formed fragment ions at *m/z* 369 and 395 via cleavage of 2 amide bonds (Fig. S1I, https://links.lww.com/STCM/A70).[28–30] Figure S1J, https://links.lww.com/STCM/A70, presents the full-scan spectra of clonidine, nifedipine, and reserpine. Reserpine produced fragment ions at *m/z* 577, 448, and 397 (Fig. S1K, https://links.lww.com/STCM/A70), clonidine at *m/z* 213 (Fig. S1L, https://links.lww.com/STCM/A70), and nifedipine at *m/z* 315 and 271 (Fig. S1M, https://links.lww.com/STCM/A70).[31–33] Collectively, these results confirm that BIP-MS can reliably identify target chemical additives through distinct molecular ion peaks and characteristic fragment ions, further validating its qualitative performance for analyte detection.

Although the primary objective of this study was the rapid qualitative screening of chemical additives in various CPM dosage forms, the quantitative capability of BIP-MS was systematically evaluated by examining key performance indicators, including linear range, precision, LOD, and LOQ, to assess the relationship between signal response and sample concentration. To minimize potential interference from isomers, characteristic fragment ions were used for quantitative analysis. All standard curves showed good correlation between ion intensity and concentration ($0.9051 \le R^2 \le 0.9984$; Supplemental Table S4, https://links.lww.com/STCM/A70), indicating reliable linearity. Precision, expressed as RSD, was below 15% for all chemical additives, except for nifedipine (RSD = 18.54%) due to its relatively low signal response. LOD and LOQ are critical metrics for evaluating rapid screening devices. Experimental results demonstrated that LODs for all target analytes were below 0.01 ppm, with caffeine and paracetamol achieving LODs as low as 0.001 ppm (Supplemental Table S4, https://links.lww.com/STCM/A70). Matrix interference is common and inevitable in direct mass spectrometric analysis of complex samples. The antimatrix interference capability of BIP-MS was further assessed, revealing that complex CPM matrices, including excipients such as starch and sucrose, as well as other chemical components, caused some ion suppression. However, due to the high ionization efficiency of BIP-MS, the MFs of the tested compounds were all greater than 70% (e.g., 80.05%, 71.63%, and 77.62% for caffeine, pioglitazone, and clonidine, respectively; Supplemental Table S5, https://links.lww.com/STCM/A70), demonstrating satisfactory antimatrix interference performance sufficient for highly sensitive and rapid screening.

3.4. Rapid screening of chemical additives in 23 CPMs using BIP-MS

To evaluate the performance of BIP-MS in real sample analysis, 23 CPMs, including 7 anticold, 8 hypoglycemic, and 8 antihypertensive formulations with diverse dosage forms and preparation methods, were analyzed to identify potential chemical additives. Five chemical additives were sensitively detected in 7 CPMs (Fig. 3), of which four were anticold formulations. Chlorpheniramine maleate, commonly added to anti-cold CPMs for its strong antiallergic effects,[34] alleviates symptoms such as sneezing, nasal congestion, nasal discharge, itching, and rash. Paracetamol, a widely used analgesic and antipyretic agent,[35] exhibits enhanced analgesic effects when combined with caffeine.[36] The primary MS spectrum of Ganmaoling revealed paracetamol (*m/z* 152), caffeine (*m/z* 195), and chlorpheniramine maleate (*m/z* 275) (Fig. 3A), with their characteristic fragment ions confirmed via CID MS^2. MS spectra of 3 other anticold CPMs are shown in Figure 3B–3D. In Tankejing, caffeine (*m/z* 195) exhibited a high ion signal intensity of 1.92×10^6 (Fig. 3B). Keteling displayed chlorpheniramine maleate (*m/z* 275) based on MS/MS data (Fig. 3C), while VC Yinqiao Tablets contained both paracetamol (*m/z* 152) and chlorpheniramine maleate (*m/z* 275) (Fig. 3D). No targeted chemical additives were detected in Xiaochaihu Granules, Tongxuan Lifei Pills, or Antiviral Oral Liquid. Among the 8 hypoglycemic CPMs, only Xiaokewan and Xiaotangling contained glibenclamide (*m/z* 494, $[M+H]^+$), a sulfonylurea drug (Fig. 3E–3F).[37] Its characteristic fragment ions (*m/z* 369 and 395) were also captured by BIP-MS, confirming its presence. The antihypertensive additive clonidine (*m/z* 230) was detected in Zhenjujiangyapian (Fig. 3G). All detected additives were consistent with CPM prescription components and are legally permitted. Supplemental Figure S2, https://links.lww.com/STCM/A70, shows the MS spectra of CPMs without chemical additives. The positive CPMs covered various dosage forms, including granules, tablets, pills, and capsules, demonstrating that BIP-MS can rapidly analyze complex, multimorphological samples. In addition to diverse dosage forms and complex matrices, CPMs may contain excipients such as coloring agents, preservatives, spices, and flavoring agents. For example, sucrose, a common excipient used for flavoring and shaping, was observed in most CPM spectra, with prominent peaks at *m/z* 365 and 381 corresponding to $[M+Na]^+$ and $[M+K]^+$ ions, respectively.[38] In summary, BIP-MS enables rapid MS data acquisition and convenient characterization of

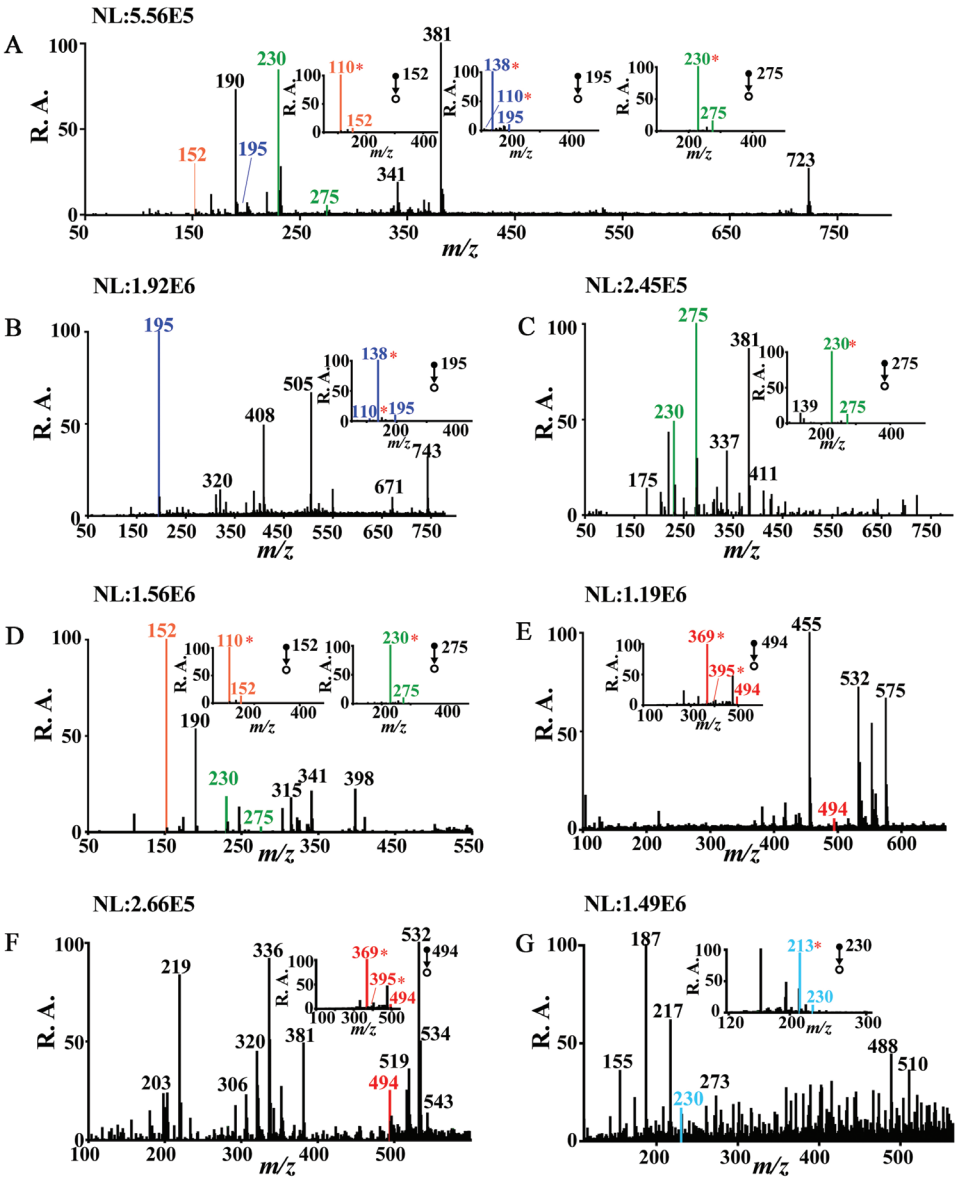

Figure 3. MS spectra of CPMs detected with chemical additives. (A) Ganmaoling (GML); (B) Tankejing (TKJ); (C) Keteling (KTL); (D) VC Yinqiao Tablets (VCYQ); (E) Xiaokewan (XKW); (F) Xiaotangling (XTL); (G) Zhenjujiangyapian (ZJJY).

target analytes in complex CPM samples with diverse formulations and matrices.

In conclusion, this study successfully developed a novel BIP-MS device for convenient and efficient screening of key target analytes in complex CPMs. BIP-MS eliminates intricate preprocessing steps while enabling rapid analysis (~10 s/sample), representing a 240-fold acceleration compared with conventional ultra-high performance liquid chromatography-high resolution mass spectrometry (UHPLC-HRMS) methods that require ultrasonic extraction and chromatographic separation (~40 min/sample).[39] The method is highly efficient, consuming minimal reagents (~10 μL/sample) and reducing solvent usage by over 95% compared with oEESI-MS (240 μL/sample).[16] Owing to its high sensitivity, BIP-MS achieves LODs below 1.0 ppb, comparable to LC-MS performance and markedly superior to traditional UPLC methods. Additionally, the cost per analysis is approximately 0.2 USD, demonstrating excellent cost-effectiveness. This technological advance offers a powerful tool for enhancing operational efficiency in on-site quality control and is expected to drive innovation in both pharmacology and TCM research.

Statement of ethics

None.

Conflict of Interest

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Data availability

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Junxian Wu and Chaofa Wei: Conceptualization, writing—original draft, writing—review and editing, and data processing. Ceyu Miao: Data processing, interpretation of result, and methodology. Jiaquan Xu, Xiang Li, and Li Zhou: Methodology, data processing, and analysis result. Shuanglong Wang: Supervision and project administration. Zidong Qiu, Liping Kang: Supervision, administration, and funding acquisition.

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