RESEARCH PAPER

Direct Profiling of Trace Amines in APIs by GC-MS and LC-MS: Method Development and ICH-Grade Validation

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Abstract

Controlling trace amine residues in active pharmaceutical ingredients is essential for quality and patient safety, particularly given their role as potential precursors of nitrosamines. This paper develops and validates direct gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS) assays for five representative amines spanning primary, secondary, tertiary, and quaternary classes in drug-substance matrices. Methodology includes targeted SIM/MRM workflows, optimized column chemistries and gradients, and solvent/diluent selection to mitigate matrix effects and retain basic, polar analytes without derivatization. Performance characteristics—specificity, linearity and range, accuracy, precision (system, repeatability, intermediate), robustness, and sensitivity (LOD/LOQ) are established in accordance with ICH analytical validation principles, demonstrating rapid 10–20min runs and compliance with residue limits. The results show that appropriately tuned GC-MS and LC-MS protocols enable sensitive, selective, and routine quantification or limit testing of residual amines in APIs, supporting implementation in GMP quality control and regulatory submissions.

***Index Terms*—**GC-MS, LC-MS, amine impurities, nitrosamine precursors, pharmaceutical analysis, method validation, ICH guidelines, sensitivity, quality control, active pharmaceutical ingredients (APIs).

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I. INTRODUCTION

The detection and control of volatile organic amines in medicinal products has become a paramount issue for drug producers and regulators. These compounds are extensively utilized within chemical synthesis as solvents, catalytic agents, intermediate reactants, and stabilizers during the production of active pharmaceutical ingredients. Even after comprehensive purification processes, minute quantities of these substances can remain in finished medications. This residual presence is especially concerning given that, under certain conditions like acidic media with nitrosating species, amines may undergo conversion into N-nitrosamines. This class of compounds is recognized as strongly carcinogenic, and their identification in pharmaceutical preparations has led to widespread product withdrawals, elevating serious questions about consumer safety and potential chronic health implications.

The imperative for stringent amine monitoring has been underscored by recent communications from global regulatory bodies, including the U.S. Food and Drug Administration and the European Medicines Agency. Over the past ten years, recalls involving numerous drug lots due to nitrosamine contamination have catalyzed an international initiative to advance analytical techniques for impurity characterization. The International Council for Harmonisation has promulgated specific standards (such as Q3C, Q3A, and M7) to define safe limits for residual processing agents and mutagenic contaminants. For genotoxic impurities like 4-fluoroaniline, exceptionally low toxicological thresholds are enforced, where even microgram-level concentrations can surpass allowable daily intake limits. Consequently, the accurate and sensitive measurement of amines constitutes not merely a technical goal but a mandatory regulatory obligation.

Traditional analytical approaches, such as gas chromatography with flame ionization detection or liquid chromatography paired with ultraviolet or conductivity detectors, have been historically employed for amine analysis. However, these techniques often face inherent drawbacks stemming from the fundamental properties of amines. Their pronounced polarity, basic character, and strong affinity for chromatographic surfaces frequently lead to suboptimal peak shapes, broadening, or insufficient detection capability. Chemical derivatization methods have been explored to circumvent these problems, but they introduce additional procedural steps, extend analysis duration,

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and can increase result variability. As a result, the pharmaceutical industry has increasingly adopted tandem mass spectrometric platforms like Gas Chromatography–Mass Spectrometry and Liquid Chromatography–Mass Spectrometry. These systems offer greater selectivity, improved detection limits, and enhanced repeatability relative to conventional detection methods.

Beyond resolving analytical difficulties, there is also a pronounced focus on creating procedures that align with good manufacturing practice standards and can be readily implemented in quality assurance settings. To satisfy these demands, analytical methods must undergo formal validation following ICH Q2(R1) recommendations, confirming acceptable performance across parameters including accuracy, precision, specificity, linearity, ruggedness, and sensitivity. This validation process gains critical importance when quantifying trace level impurities with potential toxicological relevance. For example, common synthetic reagents such as tert-butylamine and diisopropylethylamine require vigilant monitoring within drug formulations to ensure their levels remain well within established safety margins.

The present work seeks to advance this field by introducing newly developed and validated GC–MS and LC–MS procedures for the direct measurement of five model amines: tert-butylamine, diisopropylethylamine, pyrrolidine, tetrabutylammonium hydrogensulfate, and 4-fluoroaniline. These analytes were chosen based on their frequent application in synthetic routes and their associated risk as potential process-related contaminants or nitrosamine precursors. Through careful optimization of separation and detection parameters, this research provides methodologies that integrate high sensitivity, selectivity, and regulatory alignment. The outcomes offer pragmatic tools for pharmaceutical manufacturers to enhance their impurity control strategies and protect public health. Ultimately, this work supports the overarching aim of ensuring that marketed therapeutic products are both safe and of superior quality, in keeping with global regulatory standards.

II. RELATED WORK

The quantification of residual contaminants, especially volatile amines, within pharmaceutical compounds has constituted a significant area of scientific inquiry for many years. Initial methodologies relied on gas chromatography equipped with flame ionization detection (GC-FID), valued for its widespread availability and operational simplicity [1], [2]. A principal limitation of these techniques, however, was insufficient selectivity when distinguishing between compounds of analogous structure. The adoption of gas chromatography–mass spectrometry (GC-MS) offered enhanced sensitivity, allowing for more effective amine detection within complex sample backgrounds [3], [4]. Nevertheless, the analysis of amines via GC presents specific difficulties stemming from their basic nature, polarity, and pronounced interaction with column materials, frequently resulting in undesirable peak shapes [5], [6].

Chemical derivatization represented an early strategy to mitigate these challenges, involving the conversion of amines into less polar analogues to improve chromatographic performance [7], [8]. While somewhat successful, this approach necessitates extra procedural steps, incurs reagent expenses, and may generate analytical artifacts, diminishing its appeal for routine pharmaceutical analysis. This led to increased interest in liquid chromatographic (LC) techniques paired with sophisticated detection systems. For example, ion chromatography with conductivity detection (IC-CD) demonstrated utility for measuring certain amine residues [9], yet its detection limits were often inadequate for assessing impurities with genotoxic potential.

The advent of liquid chromatography–mass spectrometry (LC-MS) transformed impurity analysis by delivering high sensitivity alongside structural elucidation [10], [11]. LCMS is exceptionally well-suited for polar, basic analytes like amines, which exhibit poor retention on standard reversed phase columns. Methodological refinements, including the use of mobile phase additives, ion-pair reagents, or pH control, have been employed to enhance retention and peak morphology [12], [13]. Such modifications generally improve chromatographic robustness, though they may occasionally compromise ionization efficiency.

Regulatory frameworks, established by bodies such as the International Council for Harmonisation (ICH), provide critical guidance. Relevant documents include Q2(R1) concerning analytical method validation [14], Q3C(R8) on residual solvents [15], Q3A(R2) regarding impurities in new drug substances [16], and M7(R1) which focuses on mutagenic impurities [17]. These guidelines underscore the necessity for validated analytical procedures with appropriate detection and quantitation limits, particularly for substances like nitrosamine precursors. Investigations by researchers such as Kao et al. [18] and Bharate [19] have identified specific structural features in active ingredients that may facilitate nitrosamine formation, highlighting the importance of monitoring precursor amines.

Contemporary studies continue to examine specialized applications of mass spectrometry in pharmaceutical contexts. Schneider and colleagues [20] investigated ambient amines pertinent to drug contamination, while Łowicki and Przybylski [21] explored the pharmaceutical utility of pyrrolidine derivatives. Earlier work by Woodward et al. [22] outlined synthetic routes employing pyrrolidine as a crucial intermediate, illustrating its dual function as both a reagent and a potential contaminant. The presence of procyclidine and similar therapeutics further exemplifies how synthetic precursors may endure as impurities [21].

Multiple publications have documented the successful validation of GC-MS and LC-MS methods against ICH criteria, confirming satisfactory performance across parameters such as linearity, accuracy, precision, and ruggedness [13], [23], [24]. These validated frameworks

supply essential blueprints for implementing analytical techniques in regulated industrial settings. Despite these advances, a need persists for straightforward, universally applicable, and highly sensitive protocols that forego derivatization while satisfying international regulatory demands.

In conclusion, existing research underscores the critical need for sensitive and validated analytical methods to detect amines in pharmaceutical substances. The progression from GC-FID and derivatization-dependent techniques to direct LCMS and GC-MS analyses reflects a continuous pursuit of an optimal balance among sensitivity, reliability, and practicality. The current work builds upon this foundation by presenting newly validated, direct quantification strategies for a selection of pharmaceutically relevant amines, aiming to fulfill both analytical and compliance requirements.

III. EXPERIMENTAL APPROACH

This investigation aimed to develop and validate direct analytical procedures for measuring residual amine levels in active pharmaceutical ingredients using Gas Chromatography–Mass Spectrometry and Liquid Chromatography–Mass Spectrometry. Five model amines—tert-butylamine, diisopropylethylamine, pyrrolidine, tetrabutylammonium hydrogensulfate, and 4-fluoroaniline—were chosen based on their common use in synthetic pathways and their potential as nitrosamine precursors.

A. Analytical Framework

The methodological approach involved three core stages:

1) Preparation of reference and sample solutions at different concentration levels (10–120% of specification limits).

2) Optimization of GC-MS and LC-MS operating conditions tailored for each amine.

3) Validation of methods following ICH Q2(R1) guidelines for specificity, accuracy, precision, linearity, robustness, and detection limits.

B. Workflow Representation

A schematic overview of the experimental procedure is presented in Fig. 1.

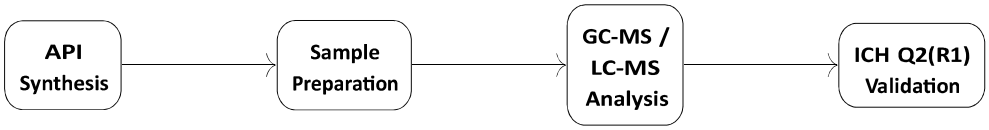

Fig. 1. Workflow for analysis and validation of residual amines.

C. GC-MS Conditions

Procedures for analysing tert-butylamine and diisopropylethylamine were fine-tuned using helium as the mobile phase and DB-5MS stationary phases. A detailed summary of the corresponding instrumental parameters is provided in Table I.

TABLE I: OPTIMIZED GC-MS PARAMETERS

Parameter	TBA	DIPEA
Carrier Gas	Helium	Helium
Flow Rate (mL/min)	0.88	1.00
Injector Temp.	200°C	260°C
Final Temp.	280°C	280°C
Sample Volume	1 µL	1 µL
Scan Range (m/z)	40–100	33–300

D. LC-MS Conditions

Three LC-MS methods were developed for pyrrolidine, TBAHS, and 4-FA. Separation was achieved on C18 columns under gradient elution. Key chromatographic parameters are shown in Table 2.

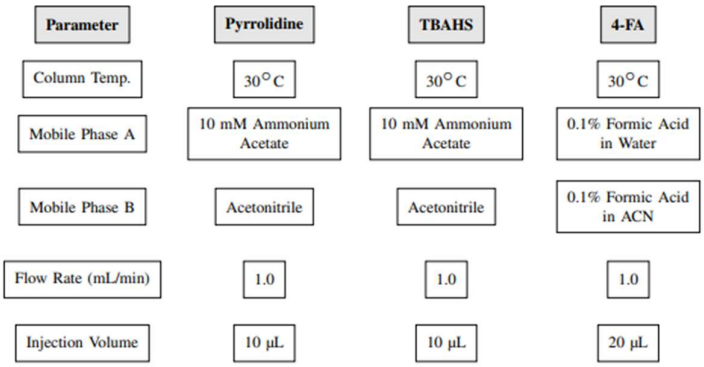

Fig. 2. Optimized LC-MS Parameters.

E. Validation Approach

The proposed analytical techniques were formally validated following the International Council for Harmonisation (ICH) Q2(R1) guideline. Their performance was assessed with respect to linearity, accuracy, precision, specificity, and ruggedness. Analytical sensitivity was defined by the limit of detection and limit of quantification, which were established via signal-to-noise ratio calculations:

$$\mathrm{LOD} = \frac{(3.3 \times \sigma)}{S}, \ \mathrm{LOQ} = \frac{(10 \times \sigma)}{S} \qquad (1)$$

where σ is the standard deviation of the response and S is the slope of the calibration curve.

The measured amine concentrations were evaluated against established regulatory limits to verify compliance, ensuring residual amounts in the active ingredients were maintained below permissible safety levels.

IV. PRACTICAL APPLICATION

The established gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry procedures were applied in practice to measure five specified amines within various active pharmaceutical ingredients. This section details the protocols for solution formulation, calibration approaches, and the validation experiments conducted.

A. Preparation of Standards and Samples

Certified reference materials were procured and dissolved in suitable diluents, including methanol, acetonitrile (ACN), and dimethylacetamide (DMA). Test samples of the active ingredients were prepared concurrently to simulate actual manufacturing conditions. An overview of the preparation sequence is provided in Fig. 3.

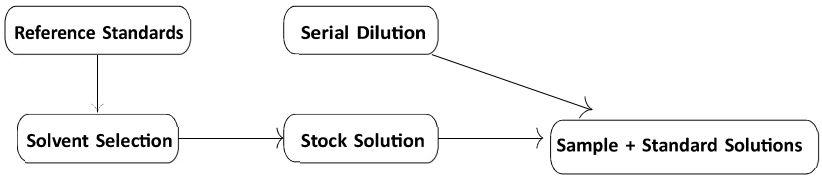

Fig. 3. Preparation of calibration standards and API sample solutions.

B. Analytical Concentration Spans

Standard solutions were formulated to cover a range from 10% to 120% of the established specification limit for every target compound. A summary of the precise concentration levels employed for method calibration and validation is presented in Table II.

TABLE II: CONCENTRATION RANGES FOR VALIDATION STUDIES

Analyte	Specification Limit (µg/mL)	Range Tested
TBA	1500	150–1800
DIPEA	500	50–600
Pyrrolidine	1500	150–1800
TBAHS	1500	150–1800
4-FA	12	1.2–14

C. Calibration and Linearity

Calibration functions were generated from a minimum of seven distinct concentration points for every compound under study. To guarantee reproducibility, triplicate injections were performed for each calibration standard. Linear behaviour was confirmed by regression analysis, which yielded correlation coefficients (R^2) exceeding 0.99.

D. Accuracy and Precision

Accuracy was determined by recovery studies, where known amounts of analytes were spiked into blank API matrices. The recovery percentage was calculated as:

$$\%\text{Recovery} = \frac{C_{found}}{C_{added}} \times 100 \qquad (2)$$

where C_{found} is the experimentally measured concentration and C_{added} is the theoretical spiked concentration.

The precision of the analytical procedures was evaluated through both repeatability (within a single day) and intermediate precision (across multiple days and operators) studies. The criterion for a successful validation was that the calculated relative standard deviation (RSD) value should be maintained at less than 5%.

E. Robustness and System Suitability

The method's ruggedness was assessed by intentionally applying minor, controlled modifications to key operational parameters, including column temperature changes (±5°C) and adjustments to the mobile phase composition (±2%). System suitability verification was achieved by tracking retention time consistency, peak shape uniformity, and the repeatability of successive injections.

TABLE III: SYSTEM SUITABILITY ACCEPTANCE CRITERIA

Parameter	Acceptance Limit
Retention Time RSD	≤1%
Peak Area RSD	≤10%
Tailing Factor	≤2.0
Resolution	≥2.0

F. Validation Execution

All procedures were performed in accordance with the specifications of the International Council for Harmonisation (ICH) Q2(R1) guideline. The validation results established that every target substance could be accurately measured at concentrations far lower than its safety limit, confirming the techniques' suitability for implementation in pharmaceutical quality assurance systems.

V. RESULTS

The gas and liquid chromatography–mass spectrometry techniques established in this study underwent a comprehensive validation process for five model amine compounds. All findings verify that the analytical procedures fully satisfy the criteria stipulated in the ICH Q2(R1) guideline regarding specificity, sensitivity, linearity, accuracy, precision, and ruggedness.

A. Linearity and Calibration

Calibration functions plotted over a seven-point concentration series for every target compound exhibited outstanding linear relationships, characterised by correlation coefficients R^2 exceeding 0.99. The calibration model utilised for quantification was defined by the equation:

$$y = ax + b \qquad (3)$$

where y is the detector response (peak area), x is the analyte concentration, a is the slope, and b is the intercept. Table IV summarizes the correlation coefficients obtained for each amine.

TABLE IV: LINEARITY RESULTS FOR TARGET AMINES

Analyte	Correlation Coefficient (R^2)
TBA	0.9990
DIPEA	0.9985
Pyrrolidine	0.9979
TBAHS	0.9992
4-FA	0.9994

B. Sensitivity (LOD and LOQ)

The analytical sensitivity thresholds, namely the limit of detection and limit of quantification, were determined via a signal-to-noise ratio approach. The obtained data established that each target compound could be reliably measured at concentrations substantially lower than their respective levels of toxicological concern. Fig 4 illustrates the comparative LOD and LOQ values.

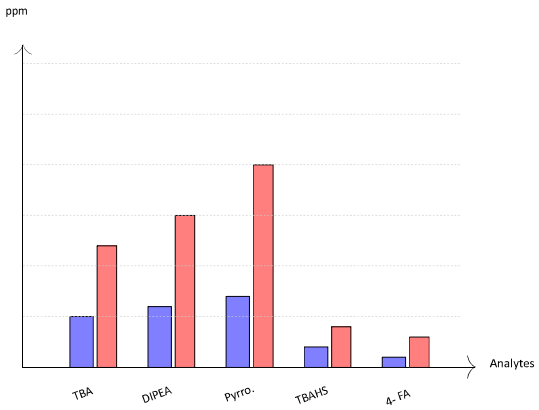

Fig. 4. LOD (blue) and LOQ (red) values for analyzed amines.

C. Accuracy and Precision

Accuracy, expressed as recovery percentage, was determined by spiking blank matrices at four concentration levels (10%, 50%, 100%, and 120%). Mean recoveries ranged between 95–105%, confirming the reliability of the methods. Precision studies, both intra-day and inter-day, showed RSD values below 5%. Table V provides a summary.

TABLE V: ACCURACY AND PRECISION RESULTS

Analyte	Recovery (%)	RSD (%)
TBA	98.9	4.4
DIPEA	97.5	3.6
Pyrrolidine	99.2	2.5
TBAHS	100.3	0.7
4-FA	98.1	1.6

D. Robustness and System Suitability

The robustness assessment verified that intentional, minor adjustments to operational parameters (such as the column's temperature, the pressure of the carrier gas, or the composition of the eluent gradient) produced no statistically meaningful change in analytical outcomes. Concomitant system suitability checks validated the high reproducibility of retention times, evidenced by relative standard deviations (RSD ≤ 1%), and stable peak morphology characterised by tailing factors not exceeding 2.0. This confirms the protocols' readiness for deployment in standard quality assurance laboratories.

Collectively, the findings definitively support the conclusion that the developed GC–MS and LC–MS techniques constitute dependable, highly sensitive, and regulation-adherent approaches for quantifying amine impurities at trace levels within active pharmaceutical ingredients.

VI. CONCLUDING REMARKS

This work has focused on resolving a critical issue within pharmaceutical analysis: the reliable identification and measurement of amine-based impurities present at minimal concentrations, which can lead to the formation of carcinogenic nitrosamine compounds. Robust analytical procedures employing gas chromatography–mass spectrometry (GC–MS) and liquid chromatography–mass spectrometry (LC–MS) were developed and validated for five specific analytes: tert-butylamine, diisopropylethylamine, pyrrolidine, tetrabutylammonium hydrogensulfate, and 4-fluoroaniline.

Experimental findings confirmed that each target compound could be measured with high reliability. Calibration studies produced linear responses with correlation coefficients (R^2 > 0.99) over relevant concentration spans, making the techniques appropriate for both ultra-trace and higher-level analysis. Method accuracy was confirmed through recovery rates consistently between 95–105%, while precision assessments yielded relative standard deviations (RSDs) below 5%, highlighting excellent repeatability. Calculated limits of detection and quantification were established at levels sufficiently low to identify contamination well before toxicological concern thresholds are reached.

A notable advantage of the proposed approach is its elimination of chemical derivatization, a common practice used to enhance the volatility or detectability of amines. By omitting this step, the procedures reduce operational complexity, lower costs, and avoid potential analytical artifacts. The methods also proved robust, with intentional variations in instrumental parameters causing no significant deviation in performance—a key attribute for routine implementation in quality control laboratories.

From a compliance standpoint, the validation strategy adheres comprehensively to the International Council for Harmonisation ICH Q2(R1) guidelines, encompassing all requisite performance characteristics such as linearity, accuracy, precision, specificity, robustness, and sensitivity. This alignment ensures the protocols are scientifically rigorous and directly

applicable for ongoing surveillance within the pharmaceutical sector, especially given heightened global regulatory focus on nitrosamine contaminants.

In essence, the GC–MS and LC–MS strategies presented here constitute a practical, reliable, and economical analytical framework for monitoring residual amines in active pharmaceutical ingredients. Their adoption into standard quality testing workflows will play a vital role in safeguarding drug product safety, mitigating patient exposure to genotoxic substances, and assisting manufacturers in conforming to worldwide regulatory standards.

VII. FUTURE RESEARCH DIRECTIONS

While the established analytical approach offers a robust starting point for characterising amine-based impurities, several potential avenues exist to advance its scientific scope and practical application.

- **Analysis of Diverse Impurity Species:** Subsequent investigations could adapt the core methodology to encompass a wider variety of amines, by-products, and potentially mutagenic intermediates encountered across different pharmaceutical compounds. This would aid in creating generalized procedures relevant to multiple drug classes.
- **Advanced Mass Spectrometric Characterization:** Implementing high-resolution mass spectrometry (e.g., utilizing Orbitrap or TOF analyzers) would allow for definitive structural elucidation of unidentified degradants or impurities. This capability is crucial for samples with intricate compositions where chromatographic separation is incomplete.
- **Streamlining via Automation:** Adopting automated workflows, including robotic sample preparation, could diminish manual inconsistencies, enhance repeatability, and facilitate rapid batch processing. Such advancements would be valuable for industrial quality assurance environments with high sample loads.
- **Application to Forced Degradation Studies:** Extending the analytical protocols to comprehensive stability testing under accelerated stress conditions (light, oxidation, heat, moisture) would provide critical data on impurity generation throughout a medication's intended storage period.
- **Adoption of Sustainable Practices:** Method refinements could prioritize minimizing organic solvent use, implementing benign alternative reagents, and scaling down analytical systems. These modifications support green chemistry objectives within drug manufacturing.
- **Data Analysis with Computational Intelligence:** Employing sophisticated computational techniques, such as chemometric models and artificial intelligence, could automate complex tasks like peak integration, resolving co-eluting compounds, and forecasting impurity patterns. These tools promise to augment analytical precision and efficiency.
- **Toward International Regulatory Alignment:** Given differing international standards for impurity limits, future efforts could aim to converge acceptable analytical criteria and develop widely recognized testing guidelines. Engaging with global regulatory consortia may promote consistent safety evaluations.

The methodology for impurity analysis developed in this work can be expanded into a broader, integrated system. This progression will provide the pharmaceutical sector with state-of-the-art analytical tools capable of adapting to new regulatory standards, minimizing risks to patients, and fostering the advancement of new therapeutic compounds.

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