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*REVIEW ARTICLE*

# ADVANCES IN GAS CHROMATOGRAPHY FOR DETECTING PROCESS IMPURITIES: A COMPREHENSIVE REVIEW ON METHOD DEVELOPMENT, VALIDATION, AND SCALABILITY

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## *Abstract*

**Background:**Gas chromatography (GC) remains a cornerstone in analytical chemistry, extensivelyemployed for the detection and quantification of process impurities, including volatile organic compounds (VOCs) and genotoxic impurities (GTIs) in pharmaceutical and industrial applications.

**Main Body:**This review examines the evolution of conventional GC techniques with a focus on method development and validation in line with International Council for Harmonisation (ICH) guidelines. Special emphasis is placed on nitrosamines, scalability, cost-benefit analysis, and the integration of advanced technologies, as these aspects are pivotal in addressing modern analytical challenges.Nitrosamines, due to their carcinogenic potential, have become a focal point of regulatory scrutiny, demanding highly sensitive methods for trace-level detection. Scalability ensures that laboratory-developed GC methods can meet industrial-scale requirements efficiently. The cost-benefit analysis underscores the balance between analytical precision and economic feasibility, which is critical for widespread adoption. Additionally, the integration of advanced technologies such as sustainable practices not only enhances performance but also aligns with evolving environmental and industrial needs.

**Conclusion:** By synthesizing recent advancements, this article highlights emerging challenges and future directions for GC's role in ensuring pharmaceutical quality and safety. Citations throughout emphasize the field's progress.



## Introduction:-

Gas chromatography (GC) stands as a powerful analytical method essential for detecting and measuring contaminants in intricate mixtures. Its extensive use in the pharmaceutical industry helps meet regulatory standards for identifying volatile organic compounds (VOCs) and genotoxic impurities (GTIs)[1, 2]. Regulatory frameworks like ICH M7 stress the importance of managing genotoxic impurities, such as nitrosamines, at extremely low concentrations. Recent research highlights the pivotal role of GC in ensuring regulatory compliance and driving advancements in methodological innovation[3].

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**Main Text**

**Introduction to Gas Chromatography**

Gas chromatography (GC) is an analytical technique that separates volatile compounds based on their interactions with a stationary phase within a column and their volatility. Since its development, GC has become a cornerstone of modern analytical science due to its precision, sensitivity, and versatility. It is widely applied in pharmaceuticals, petrochemicals, food safety, and environmental monitoring[4]. In pharmaceutical applications, GC is essential for identifying process impurities such as residual solvents, volatile organic compounds (VOCs), and genotoxic impurities (GTIs).[5, 6]. The capabilities of GC technology have been significantly enhanced through innovations like its integration with mass spectrometry (GC-MS), allowing for the identification of trace contaminants at the nanogram scale [7]. Additionally, the introduction of high-resolution GC columns has led to improved separation and examination of intricate mixtures, facilitating adherence to strict regulatory standards[8].

**Analytical Challenges and the Role of GC**

The application of GC in pharmaceutical and industrial quality control is not without challenges. These include:

**Detection of Genotoxic Impurities (GTIs)**:

Substances that can damage DNA, known as genotoxic impurities, are considered potential cancer-causing agents and must be identified at extremely low concentrations, specifically at the ppb level [9, 10].Guidelines from regulatory bodies, such as ICH M7, emphasize the necessity of employing highly sensitive and precise analytical techniques to monitor and control these impurities [11].

**Complex Sample Matrices**:

The complexity of pharmaceutical products or drug substances can lead to matrix effects that interfere with the accurate detection of GTIs. To effectively separate target compounds from complex mixtures, sophisticated sample preparation methods are essential[12]. These include techniques such as solid-phase extraction (SPE), Liquid to liquid extraction (LLP) and headspace sampling, which play a vital role in isolating the analytes of interest [13].

**Technological Demands**:

The detection of GTIs, such as nitrosamines, requires high sensitivity and selectivity. GC-MS, especially in tandem mode (GC-MS/MS), provides unmatched capabilities for analyzing trace impurities in complex matrices [14].

**Detection of Genotoxic Impurities and Nitrosamines**

Nitrosamines, a subset of GTIs, are among the most scrutinized impurities in pharmaceuticals due to their potent carcinogenicity. These compounds typically form through the reaction of nitrosating agents with secondary or tertiary amines during manufacturing or storage[15]. Notable examples include N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA).The global recall of pharmaceuticals contaminated with nitrosamines has prompted stringent regulatory action. International regulatory agencies such as The Food and Drug Administration (FDA) and The European Medicines Agency (EMA) have set permissible daily intake limits, necessitating advanced analytical techniques for their detection [16, 17]. High-resolution GC-MS and GC-MS/MS have become the methods of choice, offering sensitivity at the nanogram per milliliter level. Recent studies highlight the success of GC-MS in identifying sources of nitrosamine contamination and supporting corrective measures [18-20].

**Method Development and Validation**

The development of robust GC methods involves optimizing multiple parameters:

**Column Selection**:

In gas chromatography, selecting the right column and stationary phase is essential for effective separation of analytes. The stationary phase interacts with the target compounds, and its polarity should match that of the analytes: polar analytes interact more with polar stationary phases, while non-polar analytes separate better with non-polar phases [21]. Volatility also plays a role, as more volatile compounds require different column types. Proper column selection ensures good separation, accurate retention times, and reproducible results. Matching the stationary phase to the analytes' properties is crucial for optimal performance in chromatographic analysis [22].

**Carrier Gas Optimization**:

Carrier gas optimization in gas chromatography involves selecting the right gas for efficient separation. Hydrogen and helium are commonly used because they offer high separation efficiency and are compatible with most GC detectors. They ensure fast analysis, improve sensitivity, and help achieve reliable and reproducible chromatographic results [23, 24].

**Injection Techniques**:
Split and splitless injection methods are utilized based on sample concentration and matrix characteristics.

The validation of gas chromatography (GC) methods is critical to ensuring the accuracy, precision, and reproducibility of analytical results, particularly in regulated industries like pharmaceuticals. ICH Q2(R1) guidelines outline specific validation parameters, including linearity, which assesses the method's ability to produce consistent results over a range of concentrations, and sensitivity, which evaluates the method's capacity to detect trace amounts of analytes. Robustness testing ensures that the method remains reliable under varied conditions. Adhering to these validation requirements ensures that GC methods meet regulatory standards, providing confidence in the analytical results and supporting product quality and safety. Advanced strategies like Quality by Design (QbD) have streamlined method development, integrating risk-based approaches and statistical tools for enhanced reliability [25].

**Scalability of GC Methods**
As impurity testing often needs to be scaled up for high-throughput environments, particularly in manufacturing processes, scalable GC methods are essential. Automation in GC systems allows for continuous or batch sampling, facilitating large-scale analysis without sacrificing accuracy or precision. This scalability is particularly important in the pharmaceutical industry, where large batches of APIs need to be tested for impurity levels across multiple production cycles[26, 27, 28]. Scaling GC methods from laboratory settings to industrial applications involves addressing the following:
**Cost Efficiency**:
Balancing analytical performance with operational costs involves optimizing consumables, such as carrier gases and columns, and implementing proper maintenance protocols [29].

**Instrumentation Durability**:
Industrial GC systems are designed for prolonged use, with durable columns and enhanced cooling systems to ensure operational stability.

**Automation**:
The incorporation of robotic systems and autosamplers has improved throughput and consistency.

**High-Throughput Analysis**:
Techniques like multiplexed GC systems enable the simultaneous analysis of multiple samples, enhancing efficiency.

**Economic Considerations**
Economic factors play a crucial role in the adoption of GC techniques. While the initial investment in GC-MS systems is high, their sensitivity, specificity, and automation capabilities provide significant long-term benefits.

**Cost-benefit analyses often consider:**
**Consumables**:
Regular expenses such as carrier gases and column replacements.

**Automation**:
Reduced labour costs through automated sample preparation and data analysis.

**Regulatory Compliance**:
Avoiding penalties and recalls by adhering to stringent impurity limits justifies the cost of advanced GC techniques [30].

**Future Directions**
The future of gas chromatography (GC) in pharmaceutical analysis is poised to embrace several emerging trends, driven by the need for greater efficiency, sensitivity, and cost-effectiveness in detecting process-related impurities, including genotoxic impurities like nitrosamines. As pharmaceutical manufacturing scales up, there is a growing demand for high-throughput GC methods capable of identifying trace impurities in large batches. Advances in GC technology, such as high-resolution columns, coupled with mass spectrometry (GC-MS/MS), offer enhanced

sensitivity and selectivity, enabling the detection of even the smallest amounts of genotoxic compounds. These developments allow for rapid, reliable, and reproducible results, which are critical for meeting regulatory requirements and ensuring product safety. Moreover, automation and integration with software platforms streamline workflows, reducing manual intervention and saving both time and labour costs. In line with green chemistry principles, there is also a shift towards sustainable practices, such as using hydrogen as a carrier gas and incorporating eco-friendly stationary phases. These innovations not only make impurity testing more efficient but also lower operational costs in the long term. The combination of high sensitivity, automation, and cost-effectiveness ensures that GC remains a vital tool in pharmaceutical analysis, particularly in the detection and quantification of harmful nitrosamine impurities in drug products [31-33]

**Emerging trends in GC include:**

**Artificial Intelligence (AI)**:

Artificial Intelligence (AI) is increasingly utilized in gas chromatography to enhance analytical efficiency. Machine learning algorithms optimize chromatographic conditions, adjusting parameters like temperature and flow rate for better performance. Additionally, AI helps in interpreting complex datasets, improving data accuracy and speeding up the analysis, which supports more informed decision-making.

**Portable GC Systems**:

In pharmaceutical analysis, portable gas chromatography (GC) systems offer significant advantages for on-site quality control and rapid impurity testing. Miniaturized GC devices enable real-time analysis of active pharmaceutical ingredients (APIs) and excipients at manufacturing sites, ensuring regulatory compliance and immediate identification of contaminants, thus improving efficiency and reducing delays[34-35].

**Advanced detectors and sampling devices**:

The advancements in gas chromatography (GC), including the development of novel detectors like the barrier discharge ionization detector (BID) and innovations in sample preparation methods, such as solid-phase microextraction (SPME) and needle-based devices. These advances enhance sensitivity, accuracy, and applicability in fields like environmental, food, and pharmaceutical analysis [36].

**Sustainable Practices**:

The adoption of hydrogen as a carrier gas and the development of eco-friendly stationary phases align with green chemistry principles [37].

**Integrated Analytical Platforms**:

Combining GC with other techniques, such as liquid chromatography (LC) or spectroscopy, offers a more comprehensive analysis of complex samples [38-40].

## Conclusions:-

Gas chromatography (GC) is adapting to meet the growing complexities of impurity analysis in the pharmaceutical industry, with significant strides in automation, miniaturization, and sustainability. The integration of AI-driven analytics is revolutionizing data interpretation, enabling faster and more accurate results while reducing human error. Additionally, advancements in miniaturization are improving the accessibility and efficiency of GC systems, making them more cost-effective and user-friendly. Sustainable practices, such as the use of hydrogen as a carrier gas and eco-friendly stationary phases, align with green chemistry principles, ensuring a more environmentally responsible approach. These innovations will solidify GC's vital role in ensuring product quality, regulatory compliance, and adherence to environmental standards.

**List of Abbreviations**

**GC**: Gas Chromatography
**GTIs**: Genotoxic Impurities
**ICH**: International Council for Harmonisation
**GC-MS**: Gas Chromatography-Mass Spectrometry

**Declarations**

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Mr. Deshoju Srinu collected and analysed the data and wrote themanuscript. He is the lead author and showed strong commitment to the work. Dr. G Sampath Kumar Reddy has made critical suggestions to the conception and substantively revised the work. Dr. B Jainendra Kumar was the supporting pillar for writing manuscript and reviewed the work. All authors have read and approved the manuscript.

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