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Review Paper

Analytical Approaches for the Estimation of Volatile Impurities

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ABSTRACT

Volatile impurities (VIs), primarily residual solvents and trace contaminants, are critical quality attributes that can significantly impact the safety, efficacy, and stability of pharmaceutical products. Owing to their high volatility and low boiling points, accurate detection and quantification of these impurities remain analytically challenging. Regulatory guidelines such as ICH Q3C, USP <467>, and BP prescribe stringent limits and classification of residual solvents into Class 1 (to be avoided), Class 2 (to be limited), and Class 3 (low toxic potential).This review presents a comprehensive overview of methodologies employed for the estimation of volatile impurities, with emphasis on sample collection, preparation, and analytical determination. Sampling techniques including static and dynamic headspace analysis, solid-phase microextraction (SPME), thermal desorption, and direct injection are critically discussed with respect to their applicability to diverse matrices. Advanced analytical platforms such as headspace gas chromatography (HS-GC), gas chromatography–mass spectrometry (GC-MS), and LC-MS/MS are highlighted for their sensitivity, selectivity, and suitability for trace-level analysis.Further, key aspects of method development and validation, including specificity, accuracy, precision, and robustness, are addressed in accordance with ICH Q2(R1) guidelines. The integration of optimized sampling strategies with advanced analytical techniques provides a reliable and regulatory-compliant framework for monitoring volatile impurities. This approach ensures product quality, patient safety, and adherence to global regulatory standards in pharmaceutical analysis.

INTRODUCTION

Volatile impurities (VIs), often present as residual solvents or trace contaminants, pose significant risks to product safety, efficacy, and environmental integrity across pharmaceutical, chemical, and food industries. [1,2,3]. Their accurate detection and quantification are essential not only for ensuring consumer protection but also for meeting stringent regulatory standards such as

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ICH Q3C, USP <467>, and BP guidelines. These impurities, due to their high vapor pressure and low boiling points, are prone to loss or transformation during sampling and handling, making their analysis particularly challenging. [4,5]

To address these complexities, a range of specialized sampling and preparation techniques have been developed—each tailored to the volatility, polarity, and matrix characteristics of the target compounds. Techniques such as headspace gas chromatography (HS-GC), solid-phase microextraction (SPME), thermal desorption, and canister sampling offer robust solutions for isolating and analyzing volatile organic compounds (VOCs) from diverse matrices including solids, liquids, and gases. These methods are further supported by advanced analytical platforms like GC-MS and LC-MS/MS, which provide high sensitivity and specificity for trace-level impurity profiling.

This document outlines the materials, methods, and analytical strategies employed in the estimation of volatile impurities, emphasizing best practices in sample collection, preparation, and method validation. The goal is to establish a scientifically rigorous and regulatory-compliant framework for impurity monitoring in controlled environments. [6,7]

Volatile impurities are classified into three classes:

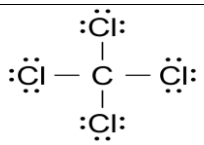
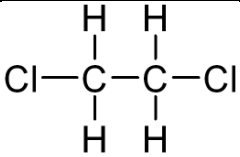
1. Class 1 – Solvents to be Avoided (Known Human Carcinogens or Environmental Hazards).
2. Class 2 – Solvents to be Limited (Toxic but less severe).
3. Class 3 – Solvents with Low Toxic Potential.[8]

Figure :1 [9,10]

ICH QC3: VOLATILE IMPURITIES

CLASS 1 (AVOID) HIGHLY TOXIC/ CARCINOGENIC	CLASS 2 (RESTRICTED) LIMITED USE ALLOWED	CLASS 3 (LOW TOXIC POTENTIAL)
Benzene	Methanol	Ethanol
Carbon tetrachloride	Acetonitrile	Acetone
1,2-dichloroethane	Chloroform	Ethyl acetate
1,1-dichloroethane	Toluene	Heptane
1,1,1-trichloroethane	cyclohexane	1-butanol

Table:1 CLASS 1 SOLVENTS AND THEIR PROPERTIES:

SOLVENTS	STRUCTURE	OCCURRENCE	LIMIT	DETECTION METHODS
Benzene		contaminant in raw materials/solvents.	2 ppm	(HS-GC), GC-MS
Carbon tetrachloride		by-product in chemical synthesis	4 ppm	HS-GC, GC-MS
1,2-Dichloroethane		in PVC production or chlorinated solvents	5 ppm	HS-GC, GC-FID, GC-MS

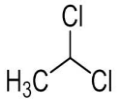
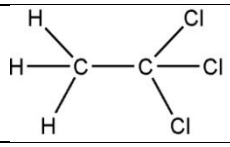
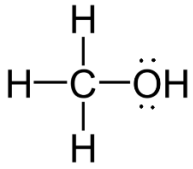
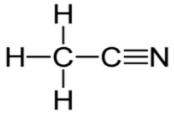
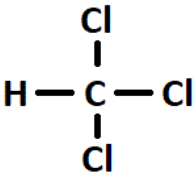
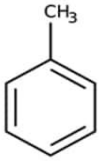
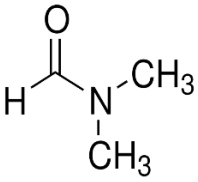
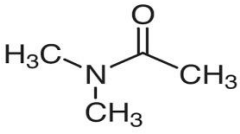
1,1-Dichloroethene		In residual monomer from PVC.	2 ppm	HS-GC, GC-MS
1,1,1-Trichloroethane		In leftover from old solvent/cleaning agents	10 ppm	HS-GC, GC-FID

Table :2 CLASS 2 SOLVENTS AND THEIR PROPERTIES:

SOLVENTS	STRUCTURE	OCCURRENCE	LIMIT	DETECTION METHOD
Methanol		Used as solvent in synthesis, extractions, and cleaning.	300	HS-GC-FID, HS-GC-MS
Acetonitrile		Common in HPLC mobile phases, synthesis, recrystallization	410	HS-GC-FID, HS-GC-MS
Chloroform		Used in organic synthesis, sometimes as a by-product.	60	HS-GC-FID, HS-GC-MS, FTIR
Toluene		Reaction solvent, recrystallization solvent.	890	HS-GC-FID, HS-GC-MS
N,N-dimethylformamide		Used in peptide coupling, polar solvent in synthesis	880	HS-GC-FID, HS-GC-MS
N,N-dimethylacetamide		Solvent for polymers, synthesis.	1090	HS-GC-FID, HS-GC-MS
Cyclohexane		Used in recrystallization, organic synthesis.	3880	HS-GC-FID, HS-GC-MS

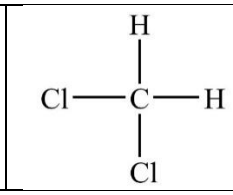
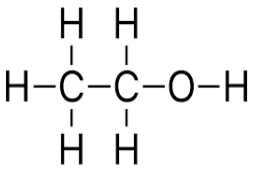
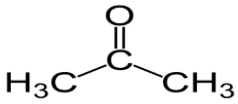
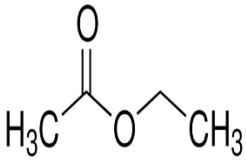
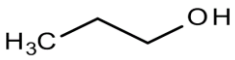
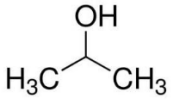
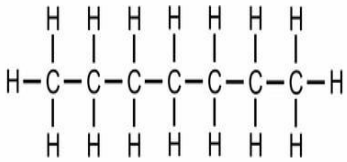
Dichloromethane		Extraction, reaction solvent, cleaning agent.	600	HS-GC-FID, HS-GC-MS

Table:3 CLASS 3 SOLVENTS AND THEIR PROPERTIES:

SOLVENT	STRUCTURE	OCCURRENCE	LIMIT	DETECTION METHOD
Ethanol		Used in formulation, extraction, and as a disinfectant	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS
Acetone		Used as a cleaning agent, extraction solvent, and in chemical synthesis	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS
Ethyl acetate		Used in extraction, chromatography, and as a flavoring agent	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS
1-propanol		Used as a solvent in the pharmaceutical industry for drug formulation.	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS
2-propanol		Used as a solvent and disinfectant in pharmaceuticals	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS
Heptane		Extraction solvent and cleaning agent	5000 ppm (≤50 mg/day)	HS-GC/FID, GC-MS

MATERIALS AND METHODS:

SAMPLE COLLECTION:

Volatile impurities are collected using methods that prevent the loss of these compounds during sampling and transport, before analysis by gas chromatography (GC) or mass spectrometry (MS). The best method depends on the sample matrix, the specific volatile organic compounds (VOCs) of interest, and the required sensitivity.

The samples used in the estimation of volatile impurities for each classes are:

Class 1 samples: APIs, Drug formulations, Excipients.

Class 2 samples: APIs, Finished drug products, Biopharmaceutical intermediates, Coatings and flavourings.

Class 3 samples: Pharmaceutical formulations, Topical formulations, Injectables & inhalations, Excipients.[11]

GENERAL CONSIDERATION OF SAMPLING OF VOLATILE IMPURITIES:

Regardless of the method chosen, several factors are critical for obtaining accurate and representative samples of volatile impurities are:

- **Material selection:** All sampling materials, including containers, tubing, and fittings, should be made of inert materials, like glass or polytetrafluoroethylene (PTFE/Teflon), that will not contaminate the sample or adsorb the target compounds.
- **Storage conditions:** Storage condition for the volatile impurities may vary to the classes:

For class 1 solvents:

*Store cool (≤ 25°C) and under inert atmosphere (e.g., nitrogen)

*Use tightly sealed amber glass or metal containers

*Place in explosion-proof flammable chemical cabinets.

For class 2 solvents:

*Store at controlled room temperature (15–25°C)

*Ensure well-ventilated storage area

*Prefer amber containers to protect from light.

For class 3 solvents:

*Store at room temperature (20–25°C)

*Use airtight standard containers

*Avoid exposure to heat and direct sunlight.[12]

THE METHODS USED FOR THE SAMPLE COLLECTION OF VOLATILE IMPURITIES ARE:

Table:4

METHOD	SUITABLE SAMPLE TYPE
Static Headspace (HS)	APIs, Tablets, Capsules, Syrups, Injectables
Dynamic Headspace (Purge-and-Trap)	Aqueous solutions, Low-level volatiles, Environmental samples
Solid-Phase Microextraction (SPME)	APIs, Tablets, Creams, Gels, Biological fluids
Direct Solvent Extraction	Excipients, Syrups, Semi-solids, Oily matrices
Thermal Desorption	Polymers, Coatings, Topicals, Solid dosage forms
Direct Injection / Dilution	Liquid formulations, Injectables, Solvent-based products
Gas Sampling (Sorbent tubes / Canisters / Bags)	Inhalation products, Aerosols, Air/Vapor samples.

Each sample collection method is selected based on the sample type, volatility of the impurities, and regulatory requirements. In that the Volatile impurities are extracted from samples using the techniques that suit the type of sample and the class of solvent being analyzed.

For drug substances, drug products, and excipients,especially those containing Class 1 or Class 2 solvents like benzene or methanol, the headspace sampling and solid-phase microextraction (SPME) methods are commonly used. These methods allow volatile compounds to be released into the gas phase and captured without

altering the sample. For intermediates and solvent mixtures, direct aqueous injection may be used when the solvents are water-soluble. For Packaging extracts and environmental samples, which may contain Class 1 or Class 2 solvents like carbon tetrachloride or THF, are often analyzed using thermal desorption or canister sampling method.For Class 3 solvents, these are considered to have low toxic potential and are generally regarded as safe when present in pharmaceutical products at levels below 5000 ppm. Solvents like ethanol, acetone, isopropanol, and butanol. These solvents are often used in formulation processes, and their presence is typically monitored in final dosage forms such as tablets, capsules, and oral liquids.Extraction of Class 3 solvents is usually performed using headspace sampling or direct aqueous injection, depending on the matrix and volatility.

SAMPLE PREPARATION:

Sample preparation for volatile impurities involves selecting a technique to isolate and introduce the volatile compounds to an analytical instrument, such as a gas chromatography.[20]
It involves selecting suitable volatile solvents for dissolving the sample, cleaning the sample to remove particles, and using techniques to increase or isolate the volatility of the desired components, such as evaporation through nitrogen blowdown or using the headspace method. Other methods include purge-and-trap, extraction, and derivatization to convert non-volatile compounds into volatile ones for analysis, often by gas chromatography.[21,22]
The choice of sample preparation depends on the sample matrix (solid, liquid, or gas), the concentration of impurities, and the specific impurities of interest. GC analysis requires the analyte to be in the gas phase before entering into the column.
The goal is to obtain a pure, volatile sample in a form that can be directly injected into the instrument for analysis, often after dilution in a volatile solvent. [23]

COMMON SAMPLE PREPARATION TECHNIQUES:

1.SOLVENT EXTRACTION:

It Involves dissolving the sample in a suitable volatile solvent (like hexane or methanol) to extract the volatile impurities. This is a common method for both solid and liquid samples.[24,25,26]

2.SOLID PHASE MICROEXTRACTION:

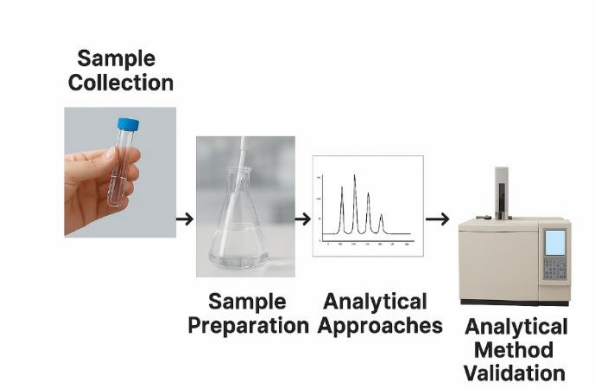
A solvent-free technique where a coated fiber is exposed to the sample to absorb and concentrate target analytes, which are then desorbed directly into the GC.[27]

3.HEADSPACE ANALYSIS:

There are two types of headspace analysis techniques are;
1.Static Headspace: The sample is placed in a sealed vial and heated to vaporize the volatile compounds, which collect in the empty space (headspace) above the sample.
2.Dynamic Headspace: Volatile compounds from the sample are concentrated onto a sorbent trap by pumping the headspace gas through it.[28,29,30]

4.PURGE-AND-TRAP TECHNIQUE:

This method is Similar to dynamic headspace but often used for aqueous samples, where a gas is bubbled through the sample to remove volatile organic compounds (VOCs), which are then captured on a sorbent trap.[31,32,33]
Figure :2 [34,35,36,37,38]



ANALYTICAL APPROACHES FOR VOLATILE IMPURITIES:

Analytical approaches for volatile impurities refer to the systematic methods used to detect, identify, quantify, and control trace-level volatile compounds. It begins with selecting the most suitable technique based on the volatility, polarity, and nature of the sample matrix.[39]

Appropriate sample preparation strategies such as headspace analysis, solid-phase microextraction (SPME), or direct injection are then applied. Method development focuses on optimizing key parameters like temperature, carrier gas flow rate, and column selection to achieve the best resolution. [40,41]

Each method undergoes validation to confirm specificity, sensitivity, accuracy, and robustness, ensuring reliable results. Finally, the approach must align with regulatory guidelines such as ICH, USP, and BP standards to meet industry compliance requirements. [42,43,44]

Headspace GC (HS-GC) is used for quantifying residual solvents with matrix-free sampling, while GC-MS provides high specificity for identifying unknown impurities. SPME-GC enables solvent-free, non-invasive sampling of trace volatiles, making it suitable for packaging and environmental studies. Thermal Desorption GC allows direct analysis of VOCs from materials or containers without sample preparation, and LC-MS/MS is applied for semi-volatile or polar impurities, especially genotoxic or reactive volatiles. Together, these methods offer a comprehensive and reliable framework for monitoring volatile impurities across industries. [45,46,47,48,49,50]

Table :5

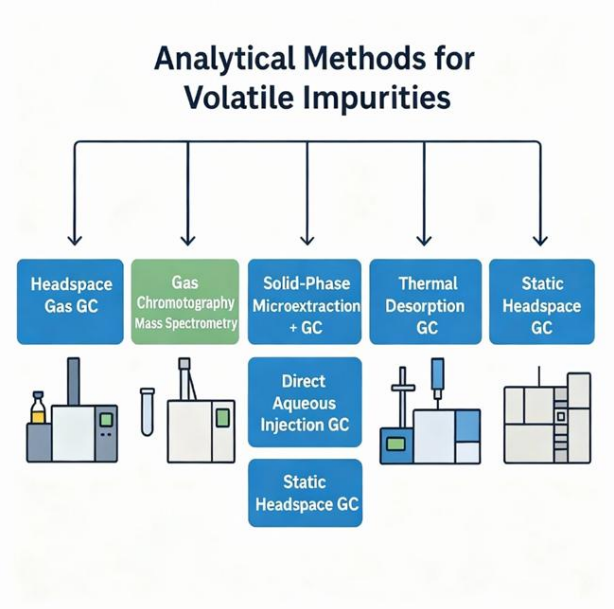
Analytical Approaches for Volatile Impurities

TECHNIQUE	PURPOSE	STRENGTHS
Headspace GC (HS-GC)	Quantification of residual solvents	Matrix-free sampling, ideal for trace volatiles
GC-MS	Identification of unknown volatile impurities	High specificity & structural elucidation
SPME-GC	Non-invasive sampling of trace volatiles	Solvent-free good for packaging or environmental
Thermal Desorption GC	VOCs from materials or containers	Direct analysis without sample prep
LC-MS/MS	For semi-volatile or polar impurities	Useful for genotoxic or reactive volatiles

CONCLUSION

The conclusion of the analytical approach for the estimation of volatile impurities:

Figure :3 [51,52,53,54]



The estimation of volatile impurities (VIs) are critical for ensuring product safety and regulatory compliance, particularly under ICH Q3C and USP <467> guidelines. [55,56,57]

Among the most widely adopted techniques, headspace gas chromatography (HS-GC) stands out for its robustness and minimal sample preparation, with flame ionization detection (FID) or mass spectrometry (MS) offering reliable quantitation and compound identification. Solid-phase microextraction (SPME) coupled with GC-MS provides a solvent-free, highly sensitive alternative, especially effective for trace-level detection in complex matrices. Thermal desorption GC-MS further enhances sensitivity for ultra-trace impurities, particularly in air-sensitive applications. [58,59,60,61]

Direct aqueous injection (DAI), though less commonly used, remains relevant for water-soluble volatiles. Method development must account for matrix effects, analyte polarity, and detection limits, with validation parameters aligned to ICH Q2(R1) standards. These techniques, when strategically selected and optimized, from the backbone of impurity profiling in regulated environments. [62,63,64]

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