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## Unmasking the purity: reviewingsources and detection methods of organic volatile impurities

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### Abstract



Organic Volatile Impurities (OVIs) are residual solvents present in pharmaceutical products as a byproduct of the manufacturing process. These solvents, used in the creation of pharmacological compounds and excipients, often remain in trace amounts in the final medicinal formulations. Their presence is not only a matter of product purity but also of safety, as OVIs can pose significant health risks and environmental hazards. This paper delves into the classification of these residual solvents based on their toxicity levels, offering insights into which solvents are most hazardous and thus require stringent control. It emphasizes the importance of meticulously analyzing these impurities as a critical aspect of quality control in drug production. Additionally, the discussion extends to the methods typically employed for evaluating OVIs, highlighting the limitations of standard production techniques in completely removing these solvents. This leads to a consideration of strategies for minimizing the use of organic solvents in pharmaceutical manufacturing, an essential step towards safer and more sustainable practices. The paper concludes with a look at future trends in detecting and managing OVIs, indicating ongoing developments in this important area of pharmaceutical research and quality assurance.

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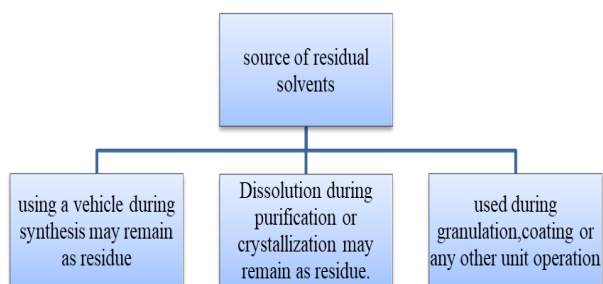
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### INTRODUCTION

Chemicals used or produced during the production of active pharmaceutical ingredients (APIs), excipients, and drug products are referred to as residual solvents in the pharmaceutical industry. Organic solvents are essential for the production of drug substances and excipients (e.g., for reaction, separation, and purification) as well as for the formulation of drug products (such as granulation and coating).

Certain organic solvents are frequently utilized to improve yield, boost solubility, or facilitate crystallization when creating pharmaceutical components, excipients, or medicinal products. However, it is not possible for these process solvents to be entirely eliminated using common manufacturing techniques, such as vacuum drying and freeze-drying. Thus, drug substance materials may contain some residual solvents. OVIs can contaminate products during packaging, storage in warehouses, or transportation. Typically, the final purification step in many pharmaceutical drug-substances processes involves a crystallization step, wherein the crystals formed can entrap a finite amount of solvent from the mother liquor, potentially causing degradation of the drug [1].

Although solvents are essential to the manufacturing of medications, there is a drawback: a large number of the solvents utilized have toxic or environmentally dangerous qualities. It is inevitable that some solvent residue will remain in the finished product, as it is not feasible to completely remove solvent residue from a manufacturing process. The presence of these undesirable substances, even in trace amounts, may impact the stability, safety, and effectiveness of pharmaceutical medicines.



**Figure 1 Sources of Residual Solvents**

It is important to ensure that residual solvents are either completely absent from products or present in minimal amounts considered safe, as they do not offer any therapeutic advantages and may pose risks to human health and the environment. It is the duty of a drug manufacturer to ensure that any OVIs present in the finished product do not pose a risk to human health and that levels of residual solvents in pharmaceuticals do not exceed recommended safety thresholds.

When using solvents known to be excessively toxic, it is best to avoid them unless justified by a risk-benefit analysis. The level of residual solvents is regulated by national and international norms, such as those set forth by the International Conference on Harmonization and the FDA, due to their demonstrated or potential toxicity [2].

### Sources of Impurities in Pharmaceuticals

The different sources of impurities in pharmaceuticals are listed below:

1. The raw materials used in production.
2. Substances utilized in the production procedure.
3. The processes or methods used in the manufacturing process.
4. Chemical procedures of the manufacturing process.
5. Contamination of the atmosphere during production.
6. Flaws in the production procedure.
7. Intermediate products during the manufacturing process.
8. Hazards in manufacturing.
9. Unsuitable storage conditions.
10. Inadvertent replacement or intentional adulteration with ineffective or fictitious substances.
11. Decomposition of the product during storage.

### Residual Solvent Analysis in Pharmaceuticals [3]

Residual solvent analysis is a crucial component of quality control for pharmaceutical ingredients used in clinical or preclinical studies, as well as in commercial medicinal products. This analysis is required for several reasons, including:

1. Organic or residual solvents with high toxicity levels pose a risk to human health.
2. Residual organic solvents can influence the physicochemical characteristics of the bulk drug material, affecting its crystalline nature and potentially causing variations in its dissolving characteristics and issues with the final product's formulation.

- Leftover organic solvents can lead to customer complaints by altering the final product's color and causing odor issues.
- The primary use of residual solvent testing is often as a checkpoint for further drying of pharmaceuticals in bulk or as a finished product.
- Testing for solvent content in intermediates may be necessary if a critical amount of residual solvents left in the intermediate can affect the following stage of the process.

### Classification of Residual Solvents [4]

OVI are categorized into three classes based on their hazardousness and environmental concerns:

- Class 1 solvents, or solvents that should be avoided, include those posing environmental hazards and substances known or highly suspected of causing cancer in humans.
- Class 2 solvents, or solvents that must be used with caution, include non-genotoxic animal carcinogens and potential triggers for other irreversible toxicity, such as neurotoxicity or teratogenicity.
- Class 3 solvents, or solvents with low hazardous potential, are those that don't require a health-based exposure limit due to their low toxic potential to humans. PDEs for class 3 solvents are 50 milligrams (mg) or more per day.
- Class 4 solvents: No sufficient toxicological information was found for these solvents, making it impossible to establish a PDE (permissible daily exposure).

### Limits of Residual Solvents [6][7]

Avoid using solvents: Solvents in class 1 (**Table 1**), due to their unacceptable toxicity and harmful effects on the environment, should not be used in the production of drug substances, excipients, or drug products. Their levels should be limited as indicated in **Table 1** unless there is an exceptional reason to use them, such as when creating a drug product with a major therapeutic advance. The solvent 1, 1-trichloroethane is included in **Table 1** due to its environmental risks. A reassessment of

the safety data led to the establishment of 1,500 ppm as the limit.

**Table 1 Solvents in Class 1 that need to be avoided**

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethane	8	Toxic
1,1,1-Trichloroethane	1500	Environmental

Solvents to be Limited: Pharmaceutical products should employ fewer solvents from class 2 (**Table 2**) due to their inherent toxicity. Permissible daily exposures (PDEs) are reported to the nearest 0.1 mg, and concentrations are reported to the nearest 10 ppm. However, these reported figures do not accurately represent the level of analytical accuracy required for determination. Precision, as part of the method's validation, needs to be ascertained and confirmed.

**Table 2 Class 2 solvent (solvents to be limited)**

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	3.8	398
Chlorobenzene	4.0	355
Chloroform	0.5	59
Cyclohexane	40.7	3772
1,2-Dichloroethane	20.6	2012
Dichloromethane	7.1	595
1,2-Dimethoxyethane	1.2	99
N,N-Dimethylacetamide	12.8	1100
N,N-Dimethylformamide	7.9	891

Usually 60% m-xylene, 14% p-xylene, 9%o-xylene with 17% ethyl benzene

### Low Toxic Potential Solvents

Class 3 solvents are considered less hazardous to human health. At the concentrations typically used in pharmaceuticals, Class 3 solvents do not present known hazards to human health.

Unfortunately, many solvents in Class 3 lack extensive research on long-term toxicity or carcinogenicity. Existing research suggests they have lower toxicity in acute or short-term studies and are not genotoxic. It is generally accepted that up to 50 mg of these residual solvents per day, or 5,000 ppm or 0.5 percent under option 1, is acceptable without further justification. Higher amounts may be permissible if they are reasonable in terms of manufacturing capacity and adhere to good manufacturing practices (GMP).

Solvents classified as Class 3 (with low hazardous potential) include:

- Acetic acid
- Acetone
- Anisole
- 1-Butanol
- 2-Butanol
- Cumene
- Dimethyl sulfoxide
- Ethanol
- Ethyl acetate
- Ethyl ether
- Formic acid

#### **Chemicals with Insufficient Toxicological Information**

Manufacturers of drug ingredients, drug products, or excipients may also find the following solvents useful. Unfortunately, sufficient toxicological evidence has not been found to establish a PDE for them. Manufacturers of pharmaceutical items should provide an explanation for any remaining amounts of these solvents [8]:

Solvents for which no adequate toxicological data were found:

- 1,1-Diethoxypropane
- 1,1-Dimethoxymethane
- 2,2-Dimethoxypropane
- Isooctane
- Isopropyl ether
- Methyl isopropyl ketone
- Methyl tetrahydrofuran
- Petroleum ether
- Trichloroacetic acid
- Trifluoroacetic acid

#### **Types of Impurity [9]**

According to ICH guidelines, impurities related to APIs fall into the following categories:

1. Organic impurities, such as starting materials, process-related contaminants, intermediates, and degradation products.
2. Inorganic impurities, such as heavy metals, ligands, catalysts, and salts.
3. Solvent Residues: These are volatile organic compounds that are generated or used in the synthesis of pharmaceutical ingredients or excipients, as well as in the formulation of pharmaceutical products.
4. Additional Agents: This category includes substances such as charcoal and filter aids, which are used in the production process but can potentially introduce impurities into the final product.

#### **MATERIALS AND METHODS**

The medicine selected for this study was identified through a literature review on hepatic allopathic formulations. It is used to assess the antioxidant activity and residual volatile contaminants.

#### **Methods for Evaluating Volatile Impurities:**

Volatile impurities were assessed using gas chromatography with the direct injection method. The NuChrom 5700 system was utilized for the development and validation of the gas chromatography method. This system features a well-established temperature programming mechanism, a flame ionization detector, and a standard oven. Organic volatile impurities were separated using a capillary packed column, which was 2 meters in length and 3.170 mm in diameter, filled with a stationary phase composed of WHP (Whitehouse Scientific) with a mesh size of 0.14 mm. Data collection was facilitated by the NuChrom software. Nitrogen served as the carrier gas. Analytical grade solvents were used as standards, including methanol, ethanol, acetonitrile, acetone, ethyl acetate, hexane, butanol, and toluene, with dimethyl sulfoxide (DMSO) serving as the diluent [10].

## Gas Chromatographic Conditions

**Table 3 Gas chromatographic conditions are summarized**

Mode	Isothermal
Over temperature	240°C
Injector temperature	180°C
Detector temperature	250°C
Run time	40 min
Injection volume	2.0µl
Carrier gas	Nitrogen

### Procedures for Gas Chromatography [11]

Gas chromatography is the preferred analytical technique for identifying and measuring OVIs. There are four main methods for conducting gas chromatographic techniques for OVIs: headspace analysis, solid-phase microextraction, direct injection, and a recently developed approach known as single drop micro-extraction (SDME).

#### Direct Injection Method

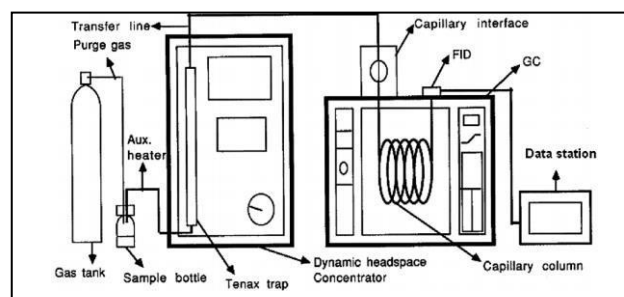
This method involves using a syringe to inject the liquid sample directly into a heated port, where it quickly vaporizes before being transferred to the capillary. The minimal cost and ease of use make this technology popular. The direct injection method offers several advantages, including reduced adsorption of active chemicals, diminished discrimination against high boiling compounds, and enhanced sensitivity for trace components. These injection techniques can also be applied to concentrated samples, often examined on splitter systems, if a solvent is added to the sample beforehand and the injection volume is kept low to avoid column overload. Solvents such as dimethylformamide (DMF), benzyl alcohol, DMSO, and water are used. A significant benefit of using a flame ionization detector (FID) is that water does not produce a solvent peak. DMF, DMSO, and benzyl alcohol, having higher boiling points, allow the solvent peak to be eluted after the analyzed residual solvent peak [12].

#### Head Space Gas Chromatography [13][14]

Headspace sampling techniques fall into two categories: dynamic and static headspace analysis. In dynamic headspace, a constant gas flow sweeps across the sample matrix's surface, transferring

volatiles from the sample matrices into a trap where the volatile residual solvent is collected. After initiating the trap's thermal desorption cycle, a carrier gas transports the analyte into a gas chromatograph for analysis.

The static headspace approach involves creating an equilibrium between the volatile components of a liquid or solid sample and the surrounding gas phase in a sealed vessel. Aliquots of the gas phase are then introduced into the gas chromatograph for analysis. This method, known as headspace gas chromatography (HS-GC), is extensively used in forensic, clinical, food, and aroma analysis fields. It is the preferred method for controlling residual solvents in pharmaceuticals and is recognized in the USP and PhEur pharmacopoeias (USA and Europe). HS-GC is advantageous for its robustness, as it introduces less dissolving liquid into the column. Both dynamic and static HS analysis can prevent the sample and gas from reaching equilibrium and allow for easy cleanup of a sample before GC analysis. It is particularly useful for samples that are incompatible with syringe handling, such as solids or highly impure materials. However, HS-GC has limitations, including low detection limits for boiling volatile and semi-volatile substances due to their low partition in the gas headspace volume. It is also ineffective for dissolving solvents trapped within crystals, limiting its sensitivity to ppm levels. Multiple headspace extractions can be used to obtain the total organic volatile impurity content, free from matrix effects. In line with **Figure 1**.

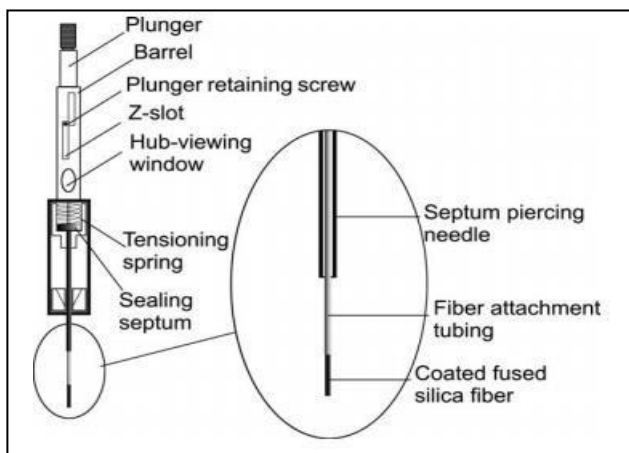


**Figure 2 Schematic diagram of a dynamic headspace device coupled to a gas chromatography**

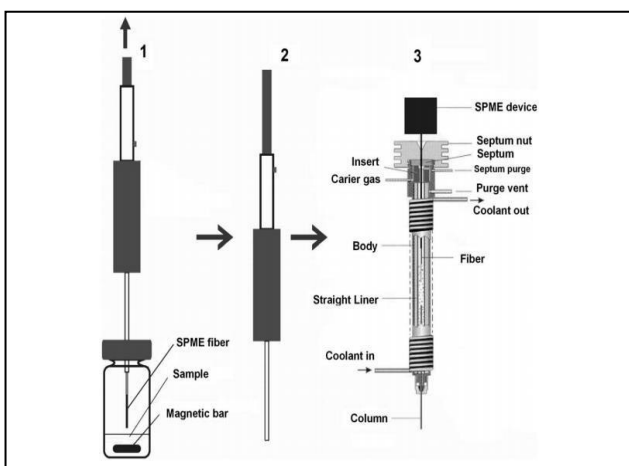
#### Solid Phase Micro Extraction (SPME):

In this method, an organic analyte is directly extracted from the sample headspace in closed vials and applied onto fused silica fiber coated with polydimethyl-siloxane, polyacrylate, or

another polymeric liquid phase. After equilibration, the fiber with the adsorbed or absorbed analyte(s) is extracted and thermally desorbed in the hot injector of a GC, using the appropriate column and detector, either with or without cryofocusing. This simple and quick procedure does not require any organic solvents for sample preparation or cleanup. SPME is particularly effective for analyzing polar residual solvents in pharmaceutical preparations and is crucial for developing accurate, sensitive, and stable methods for analyzing chemicals with varying polarity and volatility [15]. SPME, initially proposed by Pawliszyn as a solvent-free alternative for extracting organic compounds from water samples, has recently gained popularity for identifying organic contaminants in medicinal compounds. According to **Figure 3**



**Figure 3 Schematic Diagram of an SPME Device**



**Figure 4 Schematic Diagram of Headspace SPME**

**Loss on Drying (LOD)**

This method calculates the amount of volatile components released from a sample under specified vacuum or temperature conditions based on loss upon drying. The primary limitation of LOD is its generic nature. Challenges such as environmental humidity can impact the experimental results, and significant amounts of material (often 1g or more) are needed for the test to reach a detection limit of less than 0.1% (w/w) [16].

**Thermogravimetric Analysis (TGA)**

TGA measures the loss of volatile components from a sample when exposed to a temperature gradient. A limitation of these techniques is their inability to speciate and account for volatile substances trapped in the compound's lattice structure. With just a few milligrams of the material, a detection limit of approximately 100 ppm can be achieved [17].

**Table 4 Thermo gravimetric analysis: A few milligrammes of the sample are all that are needed to achieve a detection limit of 100ppm**

Solvents	ICH Q3C Class	Ppm limit according to ICH
Methylene chloride	2	600
Chloroform	2	60

**Methods for Spectroscopy and Spectrometry:**

These methods, while applicable to ICH class 2 and class 3 solvents, typically lack the low detection limits required for hazardous residual solvents. Infrared spectroscopy shows detection limits above 100 ppm at concentrations of residuals [18].

**Table 5 Generally well as spectrometric techniques lacked the low detection limit for hazardous solvents**

		Ppm limit according to ICH
Tetrahydrofuran	2	-
Dichloromethane	2	600
Benzene	1	2
Toluene	2	890
Acetone	3	-
Ethyl ether	3	-

### How to Stay Away from Organic Solvents

Efforts are ongoing in the pharmaceutical industry to reduce the use of organic solvents in the production of pharmaceutical products and the synthesis of APIs. Manufacturers are adopting practices from greener industries to minimize their solvent use, substituting more hazardous solvents with safer alternatives with similar properties (e.g., replacing benzene with toluene) and exploring novel concepts. Potential reaction media being considered include water, supercritical fluids, clay surfaces or interiors, zeolites, alumina, fluorinated phases, silica gels, and ionic liquids [19].

### Future Trends

Gas chromatography (GC) continues to be a widely used analytical method for identifying volatile contaminants in pharmaceuticals. The introduction of new methods like SPME has rejuvenated residual solvent analysis. SPME, particularly when used with GC/MS equipment, has shown exceptional applicability in detecting unidentified volatile contaminants in medications. The industry anticipates further research into integrating SPME-based extraction processes into routine volatile impurity screening for pharmaceutical formulations [20].

### CONCLUSION

Eliminating residual solvents from pharmaceutical production processes is crucial due to their potential harm and adverse effects. Residual solvent levels in finished pharmaceutical products, especially in later stages of processing, must be closely monitored. While complete removal of these solvents is not possible, leaving remnants in the finished products, even minute concentrations can negatively impact human health and product quality. Techniques such as gas chromatography, SPME, loss on drying, and thermogravimetric analysis are employed to remove residual solvents.

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### Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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