

From Limits to Detection: Gas Chromatography as a Tool for Residual Solvents Analysis

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ABSTRACT

Residual solvents are the undesired substances (solvents) used or produced during the manufacture of a excipients, drug or pharmaceutical formulation and are not completely removed by practical methods in the final finished product. These solvents can be toxic in nature. Therefore, analysis of residual solvents becomes a necessary tool for the quality control of pharmaceuticals. The acceptable limits for these substances are given in ICH guidelines (Guideline for Residual solvents, Q3C). The intension of this paper is to review toxic limits of residual solvents and to discuss various Gas Chromatographic (GC) techniques to analyze about all the residual solvents mentioned in ICH guidelines, Q3C. Gas Chromatography is coupled with various other techniques to increase the sensitivity of the method. Various analytical techniques included in this study are gas chromatography, direct injection method, headspace gas chromatography(HSGC), static headspace sampling, dynamic headspace sampling, fast gas chromatography, headspace gas chromatography coupled flame ionisation detector (HSGC-FID), head space gas chromatography-mass spectrometry (HSGC-MS), flow- modulation technique for gas chromatography, thermal desorption- headspace gas chromatography (TD-HSGC), headspace gas chromatography- solid phase microextraction (HSGC-SPME), dual column gas chromatography, multiple headspace-single drop microextraction (MHS-SDME) and headspace gas chromatography- solid phase microextraction- mass spectrometry (HSGC-SPME-MS). Application of various gas chromatographic techniques for the quantification of a few drugs or pharmaceutical preparations are also covered under this review.

KEY WORDS: Residual solvents, Direct injection, Head-space sampling, SPME-GC, SDME-GC.

I. INTRODUCTION

As per ICH (Q3C) Guidelines, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are utilised or generated during the manufacture of drug substances or excipients, or the formulation of pharmaceutical products[1]. They can also be present in the production of raw materials required for the production of pharmaceutical drug products. Limits for the levels of residual solvents in pharmaceutical products have been set by the International Council for Harmonization of Technical Requirements for Pharmaceutical and Human Use (ICH) [2,3]. Residual solvents are classified into three categories. Class 1 solvents should be avoided as they are either confirmed or suspected human carcinogens, environmental hazards, or both. Class 2 solvents, while not genotoxic impurities, have toxicity thresholds that must be maintained within specified limits in pharmaceutical products. Class 3 solvents present the lowest risk and are permitted at a maximum concentration of 5000 ppm[4,5].

Pharmaceutical manufacturers use various organic solvents, making residual solvent analysis complex. Routine quality control often detects unknown solvents, and existing methods may lead to errors. Thus, a fast and sensitive technique is needed to identify and quantify all residual solvents in pharmaceuticals. [6].

Classification of Residual Solvents by Risk Assessment and their limits

USP is aligned with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals

for Human Use (ICH) Harmonised Tripartite Guideline for Residual Solvents Q3C (R5) approach for the classification of residual solvents. These solvents were evaluated for their possible

risk to human health and were placed into one of three classes based on their toxicity data and their environmental impact [7].

Residual solvents classes	Assessment
Class 1 (solvents to be avoided)	<ul style="list-style-type: none"> • Known human carcinogen. • Strongly suspected human carcinogen. • Solvents particularly to have ozone depleting properties • Concentration limits 2-8 PPM, except 1,1,1-trichloroethane 1500 PPM.
Class 2 (solvents to be limited)	<ul style="list-style-type: none"> • Nongenotoxic animal carcinogens • Irreversible toxicity, such as neurotoxicity or teratogenicity • Solvents suspected of other significant but reversible toxicities. • Concentration limits 50-3880 PPM.
Class 3 (solvents with low toxic potential)	<ul style="list-style-type: none"> • Solvents with low toxic potential to humans • No health-based exposure limit is needed • Concentration limits 5000 PPM.

Table1. Classification of residual solvents

There are three potential sources of residual solvents in the pharmaceutical drug products and dietary supplement products that should be considered

- Drug substance or dietary active ingredient
- Excipients and/or dietary ingredient
- Formulation

When evaluating solvents LTBP, it is necessary to consider the possible presence of additional solvents as impurities in the solvents employed. All potential sources of benzene and other Class 1 solvents must be considered due to their high toxicity. Potential sources of benzene include its synthesis as a chemical by-product, its use as a starting material, or its presence as an impurity in a solvent employed in the manufacturing process. Pharmaceutical drug products and dietary supplement products should not contain higher levels of residual solvents than can be supported by safety data. Solvent screening may be used if the user lacks the information necessary to conduct a comprehensive assessment of the potential sources of residual solvents, or as an alternative to doing so When producing drug

substances, dietary supplement ingredients, excipients, pharmaceutical drug products, and dietary supplement products, solvents that exhibit toxicity of special concern, carcinogenicity, and/or atmospheric ozone-depletion effects (Class 1) should be avoided unless their use can be compellingly supported by a risk-benefit analysis. To shield patients from potential negative effects, fewer solvents (Class 2) that are linked to less severe but still considerable toxicity should be used. Less harmful solvents (Class 3) should be used wherever possible [7].

Class 1:Solvents to be avoided

Due to their unacceptable toxicities or detrimental effects on the environment, class 1 residual solvents should not be utilized in the production of therapeutic substances, excipients, dietary additives, or official products. Unless the individual monograph specifies otherwise, their levels should be limited if their use is necessary to provide an official product with a notable therapeutic advancement. Because it poses a serious risk to the environment, the solvent 1, 1, 1-trichloroethane is listed in the Table 2 [4, 6].

Table 2. Class 1 residual solvents

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetra chloride	4	Toxic and environmental hazard
1,2-dichloroethane	5	Toxic
1,1- dichloroethane	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazard

Class 2: Solvents to be Limited

Class 2 residual solvents should be limited in drug substances, excipients, dietary ingredients, and official products because of the inherent toxicities of these residual solvents.

Permitted daily exposure (PDEs) are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm [4, 7].

Table 3. Class 2 residual solvents

Solvent	PDE (mg/day)	Concentration limit (ppm)	Solvents	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410	Methanol	30.0	300
Chlorobenzene	3.6	360	2-methoxyethanol	0.5	50
Chloroform	0.6	60	Methylbutylketone	0.5	50
Cumene	0.7	70	Methylene chloride	6.0	60
Cyclohexane	38.8	3880	N-methylpyrrolidone	5.3	530
1,2 dichloroethane	18.7	1870	Nitromethane	0.5	50
1,2 dimethoxyethane	10	100	Pyridine	2.0	200
N,N-dimethylacetamide	10.9	1090	Sulfolane	1.6	160
N,N dimethylformamide	8.8	880	Tetrahydrofuran	7.2	720
1,4-dioxane	3.8	380	Toluene	8.9	890
2-ethylene glycol	6.2	620	Trichloroethylene	0.8	80
Formamide	2.2	220	Xylene	21.7	2170
Hexane	2.9	290			

Class 3: Solvents with Low Toxic Potential

Class 3 solvents are regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. No solvent in Class 3 is

known to pose a health risk to humans at concentrations typically found in medicines (Table 4). However, many of the residual solvents in Class 3 lack long-term toxicity or carcinogenicity data.

The information that is currently available suggests that they are less harmful in short-term or acute investigations and harmful in genotoxicity studies. It is believed that for each solvent, quantities of these residual solvents of 50 mg/day or less—which, in Option 1, equates to 5000 ppm or 0.5% w/w would be acceptable without explanation. As long as they are reasonable in light of manufacturing capacity and appropriate

manufacturing practices, higher amounts might likewise be acceptable. It is necessary to identify and measure any leftover solvent if a Class 3 solvent limit in a particular monograph is more than 0.5%. When it is feasible, residual solvents should be identified, controlled, and quantified using suitable adjustments to standard solutions [4, 7].

Table 4. Class 3 residual solvents

Acetic acid	Ethyl acetate	Methyl ethyl ketone
Acetone	Ethyl ether	2-Methyl-1-propanol
Anisole	Ethyl formate	Pentane
1-Butanol	Formic acid	1-Pentanol
2-Butanol	Heptane	1-Propanol
Butyl acetate	Isobutyl acetate	2-Propanol
tert-Butyl methyl ether	Isopropyl acetate	Propyl acetate
Dimethyl sulfoxide	Methyl acetate	Triethylamine
Ethanol	3- Methyl-1-butanol	

Approaches for Determining Exposure Limits

Options for describing Limits of Class 2 Solvents

Two options are available when setting limits for Class 2 solvents[4,6].

Option 1: The concentration limits in ppm from Table 3 can be applied, calculated based on the assumption of a 10g daily administered product mass.

$$\text{Concentration (ppm)} = 1000 \times \text{PDE} / \text{Dose}$$

Here, PDE is given in terms of mg/day and dose is given in g/day. These limits apply to all substances, excipients, and products and can be used when the daily dose is unknown or variable. If all components meet Option 1 limits, they can be used in any ratio without further calculation, provided the daily dose is ≤ 10 g. For doses exceeding 10g per day, Option 2 should be considered.

Option 2: Not all components need to meet Option 1 limits. The PDE in mg/day from Table 3, combined with the maximum daily dose and equation, determines the allowable residual solvent concentration. These limits are acceptable if the solvent is minimized to the practical extent.

Residualsolvents are usually detected using chromatographic methods like gas chromatography. Class I solvents should be identified and quantified if they are likely to be present. Class II solvents must be identified and quantified if they exceed the Option 1 limits. For the presence of only Class III

solvents, a non-specific method, such as loss on drying, can be used.

Options for Describing Limits of Class 2 and Class 3 Residual Solvents

The basic requirement for Class 3 solvents (5000 ppm, or 0.5% w/w) and the concentration restrictions in ppm listed in Table 3 are applied. The following formula was used to determine the values for Class 2 solvents, assuming a product weight of 10 g supplied daily.

$$\text{Concentration (ppm)} = (1000 \mu\text{g/mg} \times \text{PDE})/\text{dose}$$

PDE is given in terms of milligrams per day (mg/day), and dose is given in grams per day (g/day). These limits are considered acceptable for all drug substances, excipients, dietary ingredients, and official products. Therefore, Option 1 may be applied if the daily amount is not known or does not exceed 10 g. If all official substances (drug substances, excipients, and/or dietary ingredients) in a formulation or dietary supplement meet the limits given in Option 1, these components may be used in any proportions. No further calculation is necessary, provided that the daily amount does not exceed 10 g. Products that are administered in doses (daily intake for dietary supplements) greater than 10 g/day are to be considered.

Reporting Levels of Residual Solvents

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in drug substances and excipients to meet the criteria. The following statements are given as acceptable examples of the information that could be provided from a supplier of drug substances or excipients to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- If Class 1 solvents are present, they should be identified and quantified.
- Only Class 2 solvents X, Y are LTBP. All are below the Option 1 limit.
- Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5%
- Only Class 3 solvents are LTBP. Loss on drying (LOD) is not greater than 0.5%.
- If only Class 3 solvents are LTBP and LOD is more than 0.5%, they should be identified and quantified.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified to allow compliance with Option 2. The term LTBP as used in the above examples refers to the solvent used or produced in the final manufacturing step and to solvents used or produced in earlier manufacturing steps and not removed consistently by a validated process[8].

Analytical methods for residual solvent analysis

The following are the most versatile methods for the determination of residual solvents [9].

Loss on drying:It was the first analytical gravimetric method for estimation of residual solvents by measuring the loss of weight up on heating sample at specified temperature typically 105-120°C for a defined time. Loss of drying is the simple and old method for determining volatile residues, but it lacks specificity and it cannot able to differentiate the residual solvents, and also high drying temperatures may lead thermal decompositions and provides inaccurate results.

Fourier transform Infrared spectroscopy (FTIR): It is used for estimation of residual solvents, such as tetrahydrofuran, dichloroethane and methyl chloride in polymer samples. The disadvantage of this method is the high detection limit (above 100 ppm) and lack of accuracy at low concentrations.

Thermogravimetric analysis (TGA): It is used to measure concentration of few mg of substance at below 100 ppm.

Differential thermal analysis (DTA)/Differential scanning calorimetry (DSC): It is more sophisticated method, which will be described more precise in determination of residual solvents.

Gas Chromatographic method: It is the specific and most widely used method for detecting and quantifying residual solvents at very low detection limits (up to ppb) due to its high sensitivity, accuracy, and ability to separate volatile compounds.

Different methods of gas chromatography

1. Direct injection

The direct injection technique introduces a liquid sample into a heated injection port via a syringe, where it vaporizes. It's ideal for samples soluble in low-boiling organic solvents, ensuring complete evaporation. Regular inspection and replacement of the injection port liner prevent poor peak shapes, column damage, and inconsistent results. While effective for residual solvent analysis in drug substances, final product analysis may require additional sample preparation. Variants include split, splitless, on-column, and programmed temperature vaporizing (PTV)[9].

- **Split injection** - It is suitable for volatile to semi-volatile compounds, dividing the sample flow between the capillary column and the atmosphere. This method provides robustness, but reduces sensitivity because of the sample splitting.
- **Splitless injection** - Split-less injection prevents carrier gas splitting, boosting sensitivity for detecting low-concentration residual solvents by transferring most of the sample to the capillary column. However, its low carrier gas flow may need peak focusing.
- **On-column injection** - On-column injection deposits the sample onto a pre-column, venting the solvent and leaving analytes for separation.
- **Programmed Temperature Vaporizing (PTV)** - the solvent evaporates at low temperature, is vented, and solutes remain on the liner wall to be transferred onto the column upon heating. PTV provides high sensitivity but requires extensive parameter optimization, making it more time-consuming than on-column injection. Both on-column and PTV systems achieve detection limits in the part-per-trillion (ppt) range.

Following the direct injection methods (split, splitless, on-column, and programmed temperature vaporizing), the flow-modulation technique offers a faster GC separation for residual solvents. Using an Agilent 6890 GC with electronic inlet pressure control and FID, two series-coupled columns of different polarity—Rtx-Stabilwax (polyethylene glycol) and Rtx-200 (trifluoropropylmethylpolysiloxane)—are connected via a four-port Gerstel Graphpack. In stop-flow mode, a valve between the columns is opened for 2–8 seconds, briefly halting or reversing carrier gas flow in the first column. This enhances resolution of overlapping analytes. The dual-column system allows simultaneous separation of polar and non-polar components, achieving complete resolution of 36 ICH Class 1 and 2 residual solvents in just 12 minutes with improved sensitivity [10].

2. Headspace Gas Chromatography (GC)

It is a technique used to analyse volatile compounds in a sample by separating the gas phase from the sample matrix. The sample is sealed in a vial and heated, allowing volatile components to equilibrate in the headspace above the sample. This gas is then injected into the GC system for analysis. The method is widely used in pharmaceutical, food, and environmental industries, particularly for detecting residual solvents and volatile organic compounds (VOCs). It minimizes contamination, reduces sample preparation, and provides high sensitivity for volatile analytes.

There are several types of headspace GC methods [11-13]. The details were provided in **Table 5**.

Table 5. Details of headspace GC methods

S. No.	Method type	Details
1	Static headspace GC	It involves heating the sample in a sealed vial and injecting a fixed volume of the headspace gas into the GC, making it a simple and commonly used technique for routine analysis.
2	Dynamic headspace GC (purge and trap)	It uses an inert gas to purge volatile compounds into an adsorbent trap, which is then heated to release concentrated analytes into the GC, offering higher sensitivity for trace-level detection.
3	Multiple headspace extraction (MHE)	It allows repeated sampling from the same vial until all analytes are extracted, useful for complex matrices.
4	Vacuum headspace GC	It reduces vial pressure to enhance the release of volatiles, increasing sensitivity for low vapor pressure compounds.
5	Equilibrium headspace GC	It ensures reproducibility by achieving equilibrium between the sample and headspace, making it ideal for quantitative analysis.

There is a fast gas chromatographic method which is in accordance with European and United States Pharmacopeias, but is faster than the compendial procedures. It uses Gas chromatograph (GC) equipped with headspace sampler and a flame-ionisation detector. Various GC parameter used for this method are inlet heater 150°C, detector 290°C, oven initial temperature 40°C maintained for 4 min, then raised at a rate of 10°C/min to 160°C, maintained for 10 min. Column used is DB-624 fused silica capillary column (1.8m × 30m × 0.32mm). Carrier gas used is Helium and injection volume is 1ml. This method is accurate, linear and precised. The solvents included in the validation comprise the five class 1 solvents, 17

class 2 solvents, 17 class 3 solvents and three unclassified solvents according to ICH guideline Q3C. This method successively been used, with only minor modifications, for many drug substances during development. Quantification limits can be adjusted, to some extent, by the amount of sample analyzed and by choosing water or Dimethyl formamide (DMF) as a diluent. Depending on the nature of the sample and the residual solvent, the presence of sample matrix may affect the response of a solvent [14].

Solvents in drug substance a generic static headspace gas chromatography method is used. This method is used for the analysis of 44 residual solvents of classes II and III of International

Conference of Harmonization guideline, Q3C. To improve the sensitivity Dimethylsulfoxide (DMSO) is selected as the sample diluent, as it has high capacity of dissolving drug substance, high stability and high boiling point. The GC parameters, e.g. sample split ratio, carrier flow rate and oven temperature gradient are manipulated to enhance the method sensitivity and separation efficiency. This method of analysis is very rapid as it has total run time of 30 min. This is an accurate, precised, linear and sensitive method. The recoveries of most of these solvents are greater than 80%, within the method determination ranges. This method is not suitable for the 10 remaining ICH classes I and III solvents, because they are too polar (e.g. Formic acid and Acidic acid), or have boiling points higher than 150 °C (e.g. Anisole and Cumene). This method has a much shorter sample equilibration time, a better separation for many solvents, a higher sensitivity and a broader concentration range [15].

3. Solid-phase microextraction (SPME)

Apart from direct injection and headspace (HS) sampling, solid-phase microextraction (SPME) has emerged as a versatile technique to address injection challenges in gas chromatography (GC). In SPME, analytes are absorbed onto a stationary phase coated on a fused silica fiber, which is housed in a protective syringe-like assembly for safe handling and injection into the GC. Once equilibrium is reached between the fiber and the liquid or headspace phase, analytes are thermally desorbed in the GC injector and transferred onto the column. Fiber selectivity can be tuned by altering the coating type or thickness based on analyte characteristics.

SPME can be performed in two modes: direct immersion, where the fiber is immersed in the liquid matrix, and headspace SPME, where volatile analytes are absorbed from the gas phase above the sample. Headspace SPME protects the fiber coating from degradation by high-molecular-weight or non-volatile interferents, making it widely used for pharmaceutical residual solvent (RS) analysis. Headspace SPME can further be classified into gas-tight SPME, which removes small headspace volumes and provides higher sensitivity for volatile compounds, and conventional headspace SPME, which offers better precision.

Coupling SPME with GC–mass spectrometry (MS) enables sensitive identification of unknown solvent residues. However, the technique requires careful and time-consuming optimization of parameters such as fiber type,

extraction mode, temperature, time, and desorption conditions. Fiber wear and inter-batch variability can affect extraction efficiency, limiting its routine applicability. Despite these challenges, SPME remains a popular technique after static HS and direct injection, particularly for accurate and precise RS identification in pharmaceuticals [16,17].

4. Single drop microextraction

Single drop microextraction (SDME), also known as Liquid Microextraction (LME), is an indirect injection technique that offers a simple, cost-effective alternative to SPME. It requires only a microsyringe and a small amount of organic solvent. This technique combines liquid extraction and solid-phase microextraction, using a small solvent drop (1-3 µL) suspended at the syringe needle tip in the headspace above the sample. The drop's surface area impacts extraction speed and efficiency, with larger drops offering higher efficiency but lower stability and reproducibility. Various solvents with different polarities can be used for extraction[9].

Modes of Gas chromatography

Gas chromatography can be operated in two different modes – separation and detection modes.

GC separation mode

GC separation typically uses capillary (narrow-bore) and wide-bore columns, which have largely replaced packed columns due to better separation capabilities and smaller sample sizes. Capillary columns are long tubes made from metal, glass, or quartz, with diameters ranging from 50 to 500 µm and lengths from 5 to 200 m. They are coated with a thick stationary phase film, often made from thermally stable polymers like polysiloxanes or resins. Some columns use small porous particles made from polymers or zeolites. Capillary columns offer low flow resistance, allowing for high efficiency and fast separations with either long columns or high mobile phase velocities. Modern capillary columns are durable, inert, and capable of operating across a wide temperature range, making them the most commonly used in GC analyses. A broad selection of capillary columns is available, with specific stationary phases tailored for applications like residual solvent analysis. Choosing the optimal column for such determinations is straightforward, as suppliers provide recommended methods for separation[5].

GC detection mode

GC detection involves several sensitive detectors, typically more than 100 times more sensitive than LC detectors, making them ideal for trace analysis. Detection methods vary from physical properties like thermal conductivity and light absorption to more specific properties like ionization potential. For residual solvent analysis, the Flame Ionization Detector (FID) is commonly used. It detects all carbon-containing molecules, except small compounds like methane and carbon monoxide, and is considered a universal detector due to its low detection limits, wide linear dynamic range, and reliability. For unknown analytes or when higher identification capability is needed, Mass Spectrometry (MS) detectors are preferred, breaking molecules into ionized fragments and detecting them based on mass-to-charge ratios. MS can achieve detection limits as low as 10^{-12} to 10^{-15} g with a linear range of about 10^5 . The Electron Capture Detector (ECD) is highly sensitive for compounds containing halogens or other electron-capturing groups. Other detectors in use include Photoionization Detectors (PID), Thermal Conductivity Detectors (TCD), Nitrogen-Phosphorus Detectors (NPD), and Fourier Transform Infrared (FT-IR) detectors, among others [18, 19].

Quantification residual solvents in a few Pharmaceutical formulations

1) Validated GC Method for Detecting Residual Solvents in Quinabut API

A simple and robust gas chromatographic method was developed and validated for the determination of residual solvents—acetone and 2-propanol—in quinabut API, an antihypertensive agent. The analysis employed a DB-624 fused silica capillary column (30 m × 0.32 mm, 3 μm film thickness) with nitrogen as the carrier gas. Optimized conditions included an injection port at 140 °C, detector at 250 °C, and a programmed oven temperature ramp from 40 °C to 215 °C. The method demonstrated good specificity, with a clear resolution of 2.07 between acetone and 2-propanol peaks. Linearity was observed across 15–180% concentration range, with regression coefficients (R) >0.9968, while LOD and LOQ were well below acceptable limits. Validated as per ICH guidelines, this method proved accurate, precise, and reliable for routine quality control of quinabut API [20].

2) Rapid GC Method for Detecting Residual Solvents in Benzyl Alcohol

A rapid and reliable gas chromatographic method was developed for determining residual solvents—benzene, chlorobenzene, and toluene—in benzyl alcohol, commonly used as a pharmaceutical excipient. Analysis was carried out using an Agilent 7700 GC system with a flame ionization detector and a DB-624 capillary column (30 m × 0.53 mm, 3 μm), employing nitrogen as the carrier gas at 2.5 mL/min. Optimized parameters included an injection port temperature of 180 °C, detector at 240 °C, and split ratio of 1:2, with DMSO as diluent. Retention times were 8.824, 11.461, and 13.467 minutes for benzene, toluene, and chlorobenzene, respectively. The method was validated through analysis of both pure standards and spiked solutions, confirming specificity, reproducibility, and compliance with regulatory standards. This straightforward technique enables accurate detection of toxic residual solvents in benzyl alcohol, supporting its quality assurance in pharmaceutical applications. [21].

3) Headspace GC Method for Sensitive Detection of Residual Solvents in Paclitaxel

A simple and sensitive headspace gas chromatographic method was developed and validated for the simultaneous determination of nine residual solvents—methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, n-hexane, ethyl acetate, tetrahydrofuran, and N,N-diisopropyl ethylamine—in paclitaxel. Separation was achieved on a DB-624 column (30 m × 0.53 mm, 3 μm) using a flame ionization detector with a gradient oven temperature program. Injections were performed in split mode (5:1), with N-methyl-2-pyrrolidinone containing 1% piperazine and water (80:20 v/v) as the diluent, ensuring good sensitivity and recovery. The method demonstrated symmetric peak shapes, resolution >2.0 between solvent peaks, and RSD values within 15%. Limits of detection and quantitation were established, with particularly low values for dichloromethane, n-hexane, and N,N-diisopropyl ethylamine. The method proved linear, precise, accurate, and robust across the tested range, making it highly suitable for routine determination of residual solvents in paclitaxel drug substance and formulations. [22].

4) Static Headspace GC for Reliable Residual Solvent Detection in Linezolid

A static headspace gas chromatographic method was developed for determining residual solvents in linezolid active substances, targeting

petroleum ether (60–90°C), acetone, tetrahydrofuran, ethyl acetate, methanol, dichloromethane (DCM), and pyridine. The method demonstrated excellent linearity with correlation coefficients (r) >0.9995 for most solvents and 0.9980 for petroleum ether. Limits of detection ranged from 0.12 µg/mL (petroleum ether) to 3.56 µg/mL (DCM), while limits of quantitation ranged from 0.41 µg/mL to 11.86 µg/mL. Accuracy was high, with recoveries between 92.8–102.5%, and precision was confirmed through low RSD values (0.4–1.3%) across both intra- and inter-day assays. The method was successfully applied to quality control analysis of three batches of linezolid, proving it to be accurate, precise, and robust. This validated approach ensures reliable monitoring of residual solvents in linezolid for pharmaceutical quality assurance. [23].

5) Validated Static Headspace GC Method for Residual Solvent Control in Cephalosporins

Impurity control, including residual solvents, is critical in pharmaceutical quality assurance and mandatory under GMP guidelines. To address this, a sensitive and validated static headspace gas chromatographic (HSGC) method with flame ionization detection was developed for cephalosporins. The method surveyed solvents used in cephalosporin synthesis and established a general protocol for their determination. Key optimized parameters included a DMA–water (1:1 v/v) diluent, equilibration at 120 °C for 5 min, helium as carrier gas, and a DB-624 equivalent capillary column (30 m × 0.32 mm × 1.8 µm). The oven was programmed between 40–155 °C with controlled split ratios and flow rates to maximize sensitivity and resolution. The method successfully quantified 11 residual solvents with recoveries between 98–103%, and strong linearity ($r = 0.995$ –1.000), except for n-hexane (0.980) and cyclohexane (0.988). Overall, this approach provides a robust and generalizable solution for monitoring residual solvents in cephalosporin APIs and formulations. [24].

6) Comprehensive HSGC Method for Multi-Solvent Analysis in Dapagliflozin Amorphous

A novel and sensitive static headspace gas chromatographic (HSGC) method with flame ionization detection was developed for quantifying 12 residual solvents in dapagliflozin amorphous. The targeted solvents included alcohols, esters, chlorinated, and aromatic compounds such as methanol, ethanol, diethyl ether, dichloromethane, toluene, and chlorobenzene. Separation was

achieved using a DB-624 column (60 m × 0.53 mm, 3.0 µm) with nitrogen as the carrier gas at 7.0 psi. N-methyl-2-pyrrolidone was selected as a diluent due to its high solubility for dapagliflozin. The method demonstrated excellent linearity with correlation coefficients >0.9936, recoveries between 97.1–103.0%, and LOQs well below ICH limits. All 12 solvents showed USP resolution values above 1.6, ensuring specificity. Validated according to ICH guidelines, the method proved precise, accurate, linear, and robust, making it highly suitable for routine quality control of dapagliflozin amorphous in pharmaceutical applications. [25].

7) Validated HS-GC Method for Residual Solvent Analysis in Bendamustine Hydrochloride

A headspace gas chromatographic (HS-GC) method was developed and validated for quantifying residual solvents—methanol, ethanol, isopropyl alcohol, chloroform, and toluene—in bendamustine hydrochloride. Analysis was performed on a Shimadzu GC-2010 system with AOC-5000 autosampler, FID detection, and a DB-624 capillary column (30 m × 0.53 mm, 3.0 µm). Operating conditions included an injector temperature of 100°C, detector at 250°C, and helium as the carrier gas at 3.0 mL/min with a total run time of 22 minutes. The oven program allowed effective separation, with retention times determined for both pure and spiked standards. Method validation showed linearity ($R^2 \geq 0.999$), acceptable recovery (84.57–118.86%), and precision (%RSD ≤ 15%). Sensitivity was confirmed through low LOD and LOQ values. Validated as per ICH guidelines, this method proved accurate, precise, linear, and robust, making it suitable for routine quality control of bendamustine hydrochloride at trace solvent levels [26].

8) HS-GC with FID for Accurate Residual Solvent Quantification in Palonosetron API

A validated headspace gas chromatographic (HS-GC) method with flame ionization detection (FID) was developed for the quantitative determination of ethanol, acetone, methanol, acetonitrile, and isopropyl alcohol in palonosetron API. The analysis employed an Agilent 7697A HS-GC system with a DB-624 column (30 m × 0.24 mm, 1.8 µm), using DMSO as the diluent. Headspace equilibrium was achieved at 100°C, with injector and detector temperatures of 200°C and 230°C, respectively. Nitrogen served as the carrier gas at 10 mL/min with a split ratio of

1:25. The oven was programmed from 40°C to 120°C at 10°C/min after a 5-minute hold. Validation as per ICH guidelines confirmed linearity ($R^2 > 0.99$) over 25–150 µg/mL, recoveries between 90–110%, and precision with %RSD <10. This simple and robust method ensures accurate and reliable quantification of residual solvents in palonosetron API for routine quality control[27].

9) Tracking Toxic Traces: Residual Solvent Analysis in Fluconazole API

This study investigated 29 class I and II residual solvent impurities in five Fluconazole API samples sourced from Algerian pharmaceutical industries, using headspace gas chromatography with flame ionization detection (HS-GC-FID). A Shimadzu GC-2010 Plus system with an AOC-5000 Plus autosampler and a MEGA-624 fused silica capillary column was employed under optimized conditions with helium as the carrier gas. Although 29 solvents were targeted, only four—toluene, dichloromethane, methanol, and acetonitrile—were detected across the samples. All APIs complied with regulatory standards, except one (F3), which contained slightly elevated toluene levels (22.6 ppm), indicating incomplete purification. The findings underscore the importance of stringent monitoring of residual solvents due to their carcinogenic and toxic potential, ensuring the safety and quality of pharmaceutical products [28].

10) Unmasking Solvent Impurities in Metronidazole: HS-GC-FID Insights

This study evaluated residual solvent impurities in six raw material samples of metronidazole available in Algeria, using headspace gas chromatography with flame ionization detection (HS-GC-FID). The system employed a silica column coated with phase G43, nitrogen as the carrier gas, and optimized conditions for effective separation of 29 class I and II solvents—compounds requiring strict monitoring due to their carcinogenic and toxic potential. Among the samples analyzed, five solvents were detected, with methanol quantified in the M2 sample at 14 ppm, slightly exceeding regulatory limits. While all other samples met safety standards, the excess methanol in M2 indicated incomplete purification, likely due to challenges in solvent removal. The study highlights HS-GC-FID as a reliable method for solvent impurity profiling and reinforces the importance of rigorous quality

control in ensuring the safety of pharmaceutical raw materials [29].

11) HS-GC-FID for Accurate Residual Solvent Analysis in Famotidine

A simple and specific headspace gas chromatography (HS-GC) method with flame ionization detection (FID) was developed to quantify residual solvents—methanol, isopropyl alcohol (IPA), acetone, and toluene—in famotidine. Using a Shimadzu GC-2010 equipped with a Teledyne Tekmar headspace sampler and a ZB-624 capillary column (30 m × 0.53 mm × 5 µm), analytes were separated under nitrogen carrier gas with split injection. Injection and detector temperatures were maintained at 220°C and 260°C, respectively, with optimized oven temperature programming. The method exhibited excellent specificity, resolution (>2), and theoretical plates (>3000). Linearity ($R^2 > 0.999$), robustness, and accuracy (%RSD <15%) were confirmed. Limits of detection and quantification ranged from 0.000779–0.00305 ppm and 0.00257–0.01007 ppm, respectively. Recovery studies ranged from 85.86–98.90%, and batch analysis showed solvent levels well below ICH limits. The validated HS-GC-FID method proved precise, reliable, and suitable for routine quality control of famotidine[30].

12) Rapid HS-GC Method for Residual Solvent Control in Radiopharmaceuticals

A fast and validated analytical method was developed for quantifying residual solvents in radiopharmaceuticals, including ^{18}F -FDG, ^{18}F -FES, ^{18}F -FLT, and ^{18}F -FMISO, which are used as tracers in positron emission tomography (PET) imaging. Residual solvents are critical impurities that can impact radio labeling efficiency, stability, and physicochemical properties, making their determination essential for quality control. The method employed direct gas chromatography injection with headspace sampling, in compliance with European Pharmacopoeia and ICH guidelines. Validation demonstrated excellent linearity ($R^2 > 0.99$), precision, accuracy, robustness, and sensitivity, with suitable limits of detection and quantification. This rapid HS-GC approach enables reliable and efficient monitoring of residual solvents, ensuring the safety, efficacy, and quality of radiopharmaceutical products used in nuclear medicine diagnostics and therapy [31].

13) SPME-GC for Residual Solvent Profiling in Co-Amoxiclav Tablets

This study focused on quantifying residual organic solvents in co-amoxiclav coated tablets using a solid phase microextraction–gas chromatography (SPME–GC) approach. Tablet coatings often involve organic solvents, and standard removal processes like heating and pressure reduction may leave trace amounts in the final product. The headspace-SPME method was optimized for temperature (50 °C) and extraction time (30 min) using a PDMS-DVB fiber to absorb evaporated solvent residues. Gas chromatographic analysis employed an oven temperature program from 38 °C to 210 °C, with an injector temperature of 210 °C and detector at 250 °C, using helium as carrier gas at 0.71 mL/min. Residual solvent content was determined by comparing retention times and peak areas with standards. Analysis revealed dichloromethane residues at 2.88 ± 0.58 ppm, demonstrating the method's effectiveness for sensitive, accurate monitoring of solvent residues in coated pharmaceutical tablets [32].

14) SPME-GC-MS/MS for Trace Phthalate Detection in Bottled Water

Phthalates, widely used as plasticizers, are recognized endocrine-disrupting chemicals that can leach from PET bottles into drinking water. A sensitive and validated method using solid-phase microextraction (SPME) in direct immersion mode combined with gas chromatography-tandem mass spectrometry (GC-MS/MS) was developed for quantifying phthalate residues. Six dialkyl phthalates—DMP, DEP, DiPP, DiBP, DnBP, and DEHP—were analyzed. Four SPME fibers were evaluated, with DVB/CAR/PDMS showing the highest extraction efficiency due to its combined polymeric and porous sorbent layers. Limits of detection ranged from 0.3 to 2.6 ng/mL. Analysis of twelve commercial PET bottled water samples revealed the presence of two to six phthalates per sample at concentrations between 6.3 and 112.2 ng/mL, with DnBP showing the highest levels followed by DEHP, DiBP, DMP, DEP, and DiPP. This method provides a reliable approach for sensitive monitoring of phthalate contamination in drinking water [33].

II. CONCLUSION

The review of residual solvents has highlighted the importance of controlling and monitoring these impurities in pharmaceuticals. The International Conference on Harmonisation

(ICH) guidelines, such as Q3C, provides a framework for the evaluation and control of residual solvents in pharmaceuticals.

Loss on drying, Infrared Spectroscopy (IR), Fourier Transform Infrared Spectroscopy (FTIR), Thermo Gravimetric Analysis (TGA), Differential Thermal Analysis (DTA) or Differential Scanning Colorimetry (DSC), and Gas Chromatography (GC) are some of the methods used in the analysis of residual solvents. The use of gas chromatography yields a sensitive and efficient result. Additionally, combining gas chromatography with other techniques like head space gas chromatography (HSGC), fast gas chromatography, head space gas chromatography coupled flame-ionization detector (HSGC-FID), headspace gas chromatography-mass spectrometry (HSGC-MS), GC flow-modulation technique, thermal desorption-headspace gas chromatography (TD-HSGC), headspace gas chromatography-solid phase micro extraction (HSGC-SPME), dual column gas chromatography, multiple headspace single-drop microextraction (MHS-SDME), and headspace gas chromatography-solid phase microextraction-mass spectrometry (HSGC-SPME-MS) all increase the sensitivity of gas chromatography. All of the leftover solvents are examined using different gas chromatographic methods. An efficient and sensitive method for identifying leftover solvents in excipients, medications, or pharmaceutical preparations is gas chromatography.

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REFERENCES

- [1]. Goodfellow K. The Analysis of Residual Solvents in Pharmaceuticals using Headspace GC. Reading Scientific Services 2018:01-02
- [2]. ICH Harmonized Guideline. Impurities: Guideline for Residual Solvents Q3C(R6), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2016: 3-21.
- [3]. ICH Harmonized Guideline. Impurities: Guideline for Residual Solvents Q3C(R8), International Council for Harmonisation of Technical Requirements for

- Pharmaceuticals for Human Use. 2021: 1-44.
- [4]. Indian Pharmacopeia. The Indian Pharmacopeia Commission. 9th Edition, Volume 1, Ministry of Health & Family Welfare Government of India, Ghaziabad, India, 2022.
- [5]. B'Hymer C. Residual solvent testing: A review of gas chromatographic and alternative techniques. *Pharm Res* 2003; 20(3):337-44. doi: 10.1023/a:1022693516409.
- [6]. Manish Kapil, Suman Lata, A Review: Residual Solvents and Various Effective Gas Chromatographic Techniques in the Analysis of Residual Solvent, *International Journal of Pharma Research & Review*, 2013; 2(10):25-40.
- [7]. UmamaheshwariD,NehaGuptaT, Kumar M,Venkateswarlu BS. A Review on Estimation of Residual Solvents by Different Analytical Methods. *International Journal of Pharmaceutical Science Review and Research*, 2021; 69(1).
- [8]. Klick Silke, SkoldAgneta. Validation of a generic analytical procedure for determination of residual solvents in drug substances, *Journal of Pharmaceutical and Biomedical Analysis*, 2004; 36: 401-409.
- [9]. Grodowska Katarzyna, Parczewski Andrzej. Analytical Methods for Residual Solvents Determination In Pharmaceutical Products, *Acta PoloniaePharmaceutica-Drug Research*, 2010; 67(1):13-26.
- [10]. Wittrig E Rebecca., Dorman L. Frank, English M. Christopher, Sacks D. Richard, High-speed analysis of residual solvents by flow modulation Gas chromatography, *Journal of Chromatography A*, 2004; 1027: 75-82.
- [11]. Snow H, Nicholas, Slack C. Gregory. Headspace analysis in chromatography, *Trends in Analytical Chemistry*, 2002; 21(19):608-17.
- [12]. Kolb B, Application of an automated Headspace gas chromatography for trace analysis by gas chromatography, *Journal of Chromatography*, 1976; 122:553-68.
- [13]. Lakatos Miklós. Measurement of residual solvents in a drug substance by a purge-and-trap method. *Journal of Pharmaceutical and Biomedical Analysis*. 2008; 47: 954-7. Doi: 10.1016/j.jpba.2008.03.009.
- [14]. Klick Silke, SkoldAgneta, Validation of a generic analytical procedure for determination of residual solvents in drug substances, *Journal of Pharmaceutical and Biomedical Analysis*, 2004; 36: 401-9.
- [15]. Chang Cheng, Shaorong Liu, Bradford J. Mueller, Zimeng Yan, A generic static Headspace gas chromatography method for determination of residual solvents in drug substance, *Journal of Chromatography A*, 2010; 1217: 6413-21.
- [16]. Raghani AR. High speed gas chromatographic analysis of residual solvents in pharmaceutical using solid phase micro extraction. *Journal of Pharmaceutical Biomedical Analysis*, 2002; 29:507-518.
- [17]. Legrand stephanie, dugayjose , vial Jerome, use of solid-phase microextraction coupled with gas chromatography for the determination of residual solvents in pharmaceutical products, *Journal of chromatography A*, 2003; 999:195-201.
- [18]. Chen K. Ted, Phillips G. Joseph, Durt William, Analysis of residual solvents by fast gas chromatography A, 1998; 811:145-50.
- [19]. Kumar Narendra, Gow G John, Residual solvents analysis by Headspace gas chromatography A, 1994; 667:235-40.
- [20]. Golembiovska O, Voskoboinik O, Berest G, Kovalenko S, Logoyda L (2021) Method development and validation for the determination of residual solvents in quinabut API by using gas chromatography. *Message 2. Pharmacia* 68(1): 53-59. Doi: <https://doi.org/10.3897/pharmacia.68.e52119>
- [21]. Panikumar A, Krishna V, Rajesh Ch, Sunitha G and Alekya V. Open Access Gas Chromatographic Assessment of Residual Solvents Present in Excipient-Benzyl Alcohol. *Journal of chromatography separation techniques*, 2016; 7. Doi: 10.4172/2157-7064.1000321.
- [22]. Noorbasha, Khaleel, and Abdul Rahaman Shaik. Determination of residual solvents in paclitaxel by headspace gas chromatography. *Future Journal of Pharmaceutical Sciences*, 2021; 7(1): 1-17. Doi: <https://doi.org/10.1186/s43094-021-00186-7>
- [23]. Feng XZ, Han GC, Qin J, Yin SM, Chen Z. Determination of Residual Solvents in

- Linezolid by Static Headspace GC. *Journal of Chromatographic Science*, 2016; 54(4):487-491. Doi: 10.1093/chromsci/bmv175.
- [24]. Gad M, Zaazaa H, Amer S, and Korany M. Static headspace gas chromatographic method for the determination of residual solvents in cephalosporins. *RSC Advances*, 2015; 5(22): 17150-17159. Doi: <http://dx.doi.org/10.1039/C5RA00125K>.
- [25]. Vijay Kumar C, Aparna P, Ravindra Kumar Y and Rajendra Reddy G. Determination of residual solvents in dapagliflozin amorphous by gas chromatography with static head space method. *Der Pharmacia Lettre*, 2016; 8(9): 349-356.
- [26]. Ramesh Babu J, Suhasini J, and Vidyadhara S. Residual Solvents in Bendamustine Hydrochloride By Headspace Chromatography. *Asian Journal of Pharmaceutical Analysis*, 2018; 8(1): 7-12. Doi: 10.5958/2231-5675.2018.00002.9
- [27]. Sunny Grace G, and Vijaya Lakshmi G. Quantitative determination of residual solvents in palonosetron API by HS-GC method. *Asian Journal of Pharm Clinical Research*, 2022; 15(2): 75-81.
- [28]. DerouichaMatmour, Khalil Fateh Eddine Hassam, Yassine Merad, HouariToumi. Analysis of 29 Residual Solvents-Impurities in Five Samples of Fluconazole API by Head Space Gas Chromatography with Flame Ionization Detector. *RHAZES: Green and Applied Chemistry*, 2023;18:24-37. DOI: <https://doi.org/10.48419/IMIST.PRSM/rhazes-v18.42362>
- [29]. DerouichaMatmour, Khalil Fateh Eddine Hassam, Yassine Merad, Nassima Hamdi ZianI. Residual solvents analysis in metronidazole raw material using head space gas chromatography, *Bulletin of Pharmaceutical Sciences Assiut University*, 2023; 46(1): 105-115. Doi: 10.21608/bfsa.2023.300769
- [30]. Sunitha A, Valli Kumari RV, and Tulja Rani G. A new validated GC-HS method for the determination of residual solvents in famotidine using FID. *International Journal of Pharmaceutical Science, Review and Research*, 2015; 31: 63-67.
- [31]. Mihon M, Tuta CS, Ion AC, Niculae D, and Lavric V. Fast method for the determination of residual solvents in radiopharmaceutical products. *Revista de Chimie*, 2017; 80: 666-670. Doi: 10.37358/RC.17.4.5526.
- [32]. DediHanwar, Tiara Nur Arsanti, RiestaPrimaharinastiti, and MochammadYuwono Analysis of Residual Solvents in Co-amoxiclav Coated Tablets Using Solid Phase Microextraction-Gas Chromatography. *ICB-Pharma 2022, AHCPS 3*, pp. 240-247, 2023. https://doi.org/10.2991/978-94-6463-050-3_20
- [33]. Mohammed Mousa Alshehri, Mohamed Ali Ouladsmame, Taieb Ali Aouak, Zeid Abdullah ALOthman, Ahmed YacineBadjahHadj Ahmed. Determination of phthalates in bottled waters using solid-phase microextraction and gas chromatography tandem mass spectrometry. *Chemosphere*, 2022; 304: 135214. Doi: <https://doi.org/10.1016/j.chemosphere.2022.135214>.