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Recent developments in residual solvent determination in pharmaceutical products

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Abstract
Organic solvents are indispensable in pharmaceutical manufacturing, where they facilitate chemical reactions, extraction, and purification. However, small amounts of these solvents may remain in drug substances or finished dosage forms as process-related impurities. Such residues do not contribute to therapeutic performance and may pose safety concerns depending on their inherent toxicity and the extent of patient exposure. To address these risks, regulatory agencies require strict monitoring and control of residual solvent levels.

Recent progress in this field has been driven by improvements in analytical technologies, increased automation, and refinement of international regulatory frameworks. Gas chromatography-based techniques—particularly static headspace gas chromatography, GC coupled with mass spectrometry, and solid-phase microextraction—have enhanced detection capability, selectivity, and operational efficiency. At the same time, revisions to the ICH Q3C guideline have strengthened toxicological risk assessment through updated solvent classification and revised exposure limits. Parallel adoption of greener solvent alternatives and sustainable manufacturing practices has further reduced reliance on hazardous solvents. Together, these advancements reflect a shift toward science-based, risk-oriented solvent control supported by robust analytical strategies.

Keywords: Residual solvents, GC / GC-MS, Headspace analysis, SPME, ICH Q3C (R8), Class 1 & Class 2 solvents, Toxicity classification, Green chemistry

Introduction [1, 2]

Solvents are widely employed throughout pharmaceutical development and manufacturing, serving as reaction media, crystallization aids, and purification agents. Despite downstream processing and drying steps, complete removal of these substances is often impractical, resulting in low-level solvent residues in final products. These residual solvents are considered process-related impurities and may raise safety concerns when present above acceptable limits.

Recognition of solvent-related risks emerged following evidence of toxicity and carcinogenicity associated with compounds such as benzene and carbon tetrachloride. Early regulatory approaches relied primarily on fixed concentration limits; however, these methods did not adequately account for variations in dosage, duration of exposure, or route of administration. Consequently, modern regulatory philosophy has transitioned toward exposure-based risk assessment, where solvent safety is evaluated using toxicological thresholds linked to patient intake.

The diversity of solvents used across manufacturing processes, combined with variability in analytical methodologies, underscores the need for harmonized regulatory guidance and reliable analytical tools. Advances in chromatographic instrumentation and regulatory science have therefore played a central role in strengthening residual solvent control within pharmaceutical quality systems.

Classification of Residual Solvents [3-4]

Residual solvents are categorized according to their toxicological properties and potential impact on patient safety. The ICH Q3C guideline groups solvents into three classes based on available toxicological and environmental data.

Class 1 solvents are associated with unacceptable toxicity or significant environmental hazards. These substances are recognized or suspected human carcinogens and should generally be avoided during pharmaceutical manufacturing. Their use is permitted only under exceptional circumstances, where a compelling therapeutic justification exists and strict limits are observed.

Examples: Benzene, Carbon tetrachloride, and 1,2-Dichloroethane

Table 1: Permissible Concentration Limits and Toxicological Remarks of Selected Solvents

Solvent Name	Concentration Limit (ppm)	Remarks
Benzene	2	Recognized human carcinogen
Carbon tetrachloride	4	Highly toxic; poses significant environmental risk
1,2-Dichloroethane	5	Toxic solvent
1,1-Dichloroethane	8	Toxic solvent
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2 solvents exhibit lower toxicity compared to Class 1 but still present potential health risks at elevated exposure levels. This category includes non-genotoxic animal carcinogens and other solvents with established toxicological thresholds. Their use is permitted under controlled conditions, with limits defined by permitted daily exposure (PDE) values.

Examples: Acetonitrile, Methanol, Chloroform, and Cyclohexane

Table 2: Permitted Daily Exposure (PDE) and Concentration Limits of Selected Solvents

Solvent Name	Permitted Daily Exposure (PDE, mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880

Class 3 solvents are considered to have relatively low toxic potential based on available toxicological data. Although these solvents are generally regarded as safer, their levels should still be minimized in accordance with good manufacturing practices.

Examples: Ethanol, Acetone, Isopropyl alcohol, and Acetic acid

Regulatory Guideline Updates [5]

The International Council for Harmonisation (ICH) was established to align technical requirements for pharmaceutical registration across regulatory regions. Under this framework, residual solvents were classified as impurities, leading to the ICH Q3C guideline, which defines acceptable solvent limits based on toxicological risk.

Ongoing revisions of ICH Q3C have incorporated updated safety data and expanded solvent classifications. Recent updates introduced cyclopentyl methyl ether and tertiary butyl alcohol as Class 2 solvents with defined permitted daily exposure (PDE) limits, while 2-methyltetrahydrofuran was placed in Class 3 due to its lower toxicity. The latest revision, Q3C(R9), also emphasized analytical suitability for volatile solvents.

The adoption of PDE-based limits represents a shift toward exposure-driven risk assessment, allowing solvent safety to be evaluated in relation to dose and route of administration. These updates underscore the dynamic, science-based approach of modern residual solvent regulation.

Permitted Daily Exposure (PDE) In Q3C(R8) [6]

The permitted daily exposure represents the maximum acceptable intake of a residual solvent based on long-term patient exposure. PDE values are derived using established safety factors and toxicological endpoints.

- **2-Methyltetrahydrofuran:** 50 mg/day
- **Cyclopentyl methyl ether:** 15 mg/day
- **Tertiary butyl alcohol:** 35 mg/day

The PDE values were developed by the relevant Expert Working Group (EWG). On 25 March 2020, ICH already published the document for public consultation. The values proposed then have been adopted as final draft document. This allows implementation to take place in the ICH regions.

Toxicity details

Methyl tetrahydrofuran was found to be non-genotoxic in a mutation assay with bacteria, human lymphocytes and rats. No data are available on carcinogenicity. Reproductive toxicity and repeated-dose toxicity were not observed. The product was classified in solvent class 3.

For cyclopentyl methyl ether, no toxicity in humans was found. Likewise, no genotoxic potential was found. Again, no data are available on carcinogenicity. No statements could be made on reproductive and developmental toxicity on the basis of data available to date. The product was classified as a class 2 solvent. For tertiary butyl alcohol, no genotoxicity was found either. The data on carcinogenicity do not allow any precise conclusions to be drawn with regard to the effect on humans, while changes in the renal tubules were found in rats. No precise statements could be made on reproductive toxicity either, but moderate transient systemic toxicity was found in rats. The product was classified as a class 2 solvent.

European Pharmacopoeia & USP Harmonization [7]

Residual solvent testing requirements are implemented through pharmacopeial standards that align closely with ICH guidance. In the United States, USP General Chapter <467> specifies analytical procedures and limits applicable to solvents used or generated during manufacturing. In Europe, the European Pharmacopoeia adopts ICH-based classifications while allowing for region-specific adaptations and additional solvent limits. Although significant harmonization has been achieved, differences in implementation timelines and compendial revisions persist. Manufacturers must therefore remain vigilant in monitoring updates across regulatory jurisdictions.

Analytical Methods for Residual Solvent Determination [8]

Early methods for residual solvent evaluation, such as loss on drying and non-specific spectroscopic techniques, lacked selectivity and sensitivity. Thermal methods offered incremental improvements but were insufficient for comprehensive solvent profiling.

Gas chromatography has become the technique of choice due to its superior resolving power and compatibility with volatile compounds. Static headspace sampling minimizes interference from non-volatile matrices and enhances method robustness. Coupling gas chromatography with flame ionization detection or mass spectrometry further improves quantification accuracy and compound identification, particularly in complex pharmaceutical matrices. Recent innovations focus on automation, microextraction techniques, and high-throughput workflows, enabling efficient analysis while meeting stringent regulatory requirements.

Table 3: Review of Literature on Residual Solvent Development

Sr. No.	Method (with Superscript Reference)	Chromatographic Conditions / Process Parameters
1	Residual Solvents Determination by HS-GC-FID in Omeprazole pharmaceutical formulations (2009) [9]	Column: DB-624 (30.0 m × 0.53 mm ID, 100% dimethylpolysiloxane); Split ratio: 1:10; Carrier gas: Nitrogen; Flow rate: 2.10 mL/min
2	Residual Solvent Analysis in Hydrochloride Salts of Active Pharmaceutical Ingredients (2009) [10]	Column: BP-624 (30 m × 0.53 mm × 0.25 µm; 4% cyanopropyl phenyl, 96% dimethyl polysiloxane); Carrier gas: Nitrogen; Detector: FID
3	Generic static HS-GC method for determination of residual solvents in drug substances (2010) [11]	Column: 624 capillary (30 m × 0.32 mm ID × 1.8 µm); Split ratio: 1:5-20; Diluent: Water-DMSO
4	HS-GC method for arterolane (RBx11160) maleate bulk drug (2010) [12]	Column: RTx-624 (30 m × 0.32 mm × 1.8 µm); Carrier gas: Nitrogen; Flow rate: 0.5 mL/min
5	Residual solvent determination in omeprazole API by HS-GC-FID (2011) [13]	Column: SPB-624 (30 m × 0.25 mm ID × 1.4 µm); Split ratio: 1:10; Carrier gas: Nitrogen; Flow rate: 1.0 mL/min
6	HS-GC method for levetiracetam API (2011) [14]	Column: SPB-624 (60 m × 0.32 mm ID × 1.8 µm); Carrier gas: Nitrogen; Flow rate: 1.5 mL/min
7	Validated GC-MS method for residual solvents in counterfeit tablets and capsules (2012) [15]	Column: Phenomenex-624 (60 m × 0.32 mm × 1.8 µm); Injection mode: Split (6.8:1)
8	Static HS-GC method for residual solvents in cephalosporins (2015) [16]	Column: G43 (30 m × 0.32 mm ID × 1.8 µm); Diluent: DMA:Water (1:1, v/v); Carrier gas: Helium
9	Optimized HS-GC method for pharmaceuticals (2015) [17]	Column: DB-624 (30 m × 0.53 mm ID × 3.0 µm); Diluent: DMSO
10	GC-MS method for Class-1 residual solve nts (2015) [18]	Column: HP-5 (30 m × 0.32 mm ID × 0.25 µm); Carrier gas: Helium; Flow rate: 1.0 mL/min; Split ratio: 1:50
11	Fast static HS-GC method for permethrin (2016) [19]	Column: DB-1 (15 m × 0.53 mm ID × 3.0 µm); Diluent: DMSO
12	GC assessment of residual solvents in benzyl alcohol excipient (2016) [20]	Column: DB-624 (30 m × 0.53 mm × 3.0 µm); Carrier gas: Nitrogen; Flow rate: 2.5 mL/min
13	Automated HS-GC system for pharmaceutical compounds (2016) [21]	Column: Capillary column for volatile organics; Carrier gas: Helium; Flow rate: 1.0-2.0 mL/min
14	GC method for azilsartan bulk drug quality control (2017) [22]	Column: OV-624; Carrier gas flow: 2.7-3.3 mL/min
15	Static HS-GC for canagliflozin API (2018) [23]	Column: DB-624 (30 m × 0.32 mm ID × 1.8 µm); Carrier gas: Nitrogen; Split ratio: 1:10
16	HS-GC for imatinib mesylate API (2019) [24]	Column: DB-624 (30 m × 0.53 mm × 3.0 µm); Solvents: DMF, DMSO, NMP; Linearity: 20-150%
17	HS-GC using deep eutectic solvents (2019) [25]	Column: DB-1 (30 m × 0.32 mm ID × 0.25 µm); Carrier gas: Helium; Flow rate: 1.0 mL/min
18	GC validation for brompheniramine maleate API (2020) [26]	Column: DB-624 (30 m × 0.32 mm ID × 1.8 µm); Carrier gas: Nitrogen; Split ratio: 10:1
19	Residual solvents in nanomedicine systems (2020) [27]	Column: HP-Innowax (30 m × 0.25 mm × 0.25 µm); Carrier gas: Helium; Flow rate: 1.0 mL/min
20	GC method for dipeptide mimetic (Gk-2) (2020) [28]	Column: CP-WAX 52 CB (50 m × 0.32 mm × 1.2 µm); Carrier gas: Nitrogen; Flow rate: 1.5 mL/min
21	HS-GC for paclitaxel (2021) [29]	Column: DB-624 (30 m × 0.53 mm); Diluent: NMP-water (80:20, v/v); Carrier gas: Helium; Flow rate: 2.5 mL/min
22	HS-GC for phenazopyridine hydrochloride (2021) [30]	Column: ZB-624 (30 m × 0.53 mm × 3.0 µm); Stationary phase: 6% cyanopropyl phenyl; Carrier gas: Nitrogen
23	Monitoring residual solvents in herbal medicinal products (2021) [31]	Column: G43 (30 m × 0.53 mm × 3.0 µm); Carrier gas: Nitrogen; Split ratio: 1:5
24	GC validation for bisoprolol fumarate (2021) [32]	Column: DB-624 (30 m × 0.32 mm × 1.8 µm); Carrier gas: Nitrogen; Split ratio: 10:1
25	GC method for racecadotril (2021) [33]	Column: DB-FFAP (30 m × 0.53 mm ID × 1.0 µm); Carrier gas: Nitrogen; Flow rate: 2.8 mL/min; Split ratio: 1:10
26	GC for quinabut API (2021) [34]	Column: DB-624 (30 m × 0.32 mm ID × 3.0 µm); Carrier gas: Nitrogen; Flow rate: 7.5 mL/min; Split ratio: 1:5
27	HS-GC-FID for itraconazole API (2022) [35]	Column: DB-624 (30 m × 0.53 mm × 3.0 µm); Carrier gas: Nitrogen
28	HS-GC for palonosetron API (2022) [36]	Column: DB-624 (30 m × 0.24 mm × 1.8 µm); Carrier gas: Nitrogen; Flow rate: 10 mL/min; Split ratio: 1:25
29	GC for gliclazide API (2022) [37]	Column: DB-624 (60 m × 0.32 mm × 1.8 µm); Carrier gas: Nitrogen; Flow rate: 3.0 mL/min; Split ratio: 1:10
30	Platform HS-GC for high-throughput analysis (2023) [38]	Column: Fused silica capillary; Injection mode: Split (40:1)
31	GC for paroxetine API (2023) [39]	Column: ZB-1 (30 m × 0.53 mm ID); Diluent: Dimethyl acetamide
32	HS-GC for metronidazole raw material (2023) [40]	Column: G43 phase (1.8 µm); Carrier gas: Nitrogen
33	HS-GC-FID for ciprofloxacin API (2023) [41]	Column: G43 phase (1.8 µm); Carrier gas: Helium; Split ratio: 1:5
34	HS-GC-FID for fluconazole API (2023) [42]	Column: G43 phase (1.8 µm); Carrier gas: Helium; Split ratio: 1:5
35	HS-GC for nano-formulations (2024) [43]	Instrument: PerkinElmer HS-GC-FID system; Carrier gas: Helium
36	Generic GC approach for APIs (2025) [44]	Column: DB-624 (60 m × 0.32 mm × 1.8 µm); Solvent boiling point range: 39.6-189 °C
37	HS-GC-FID for avibactam sodium API (2025) [45]	Linearity: $R^2 \geq 0.99$; Average recovery error ≤ 10%

Key Challenges & Industry Trends

1. Regulatory alignment timing

Harmonization between ICH, Ph. Eur., and USP is slow; while ICH updates are more frequent, compendial changes in USP/Ph. Eur. lag behind

2. Analytical efficiency vs. robustness

Generic GC methods save development time but must be demonstrated to perform reliably across different solvents and matrices.

3. Emerging solvents & green chemistry

Adoption of newer, less toxic solvents (e.g. 2-MTHF, CPME) reflects a trend toward sustainable process chemistry that reduces toxicological impact.

4. Validation complexity

Method validation must account for solvent volatility and ensure adequate precision, accuracy, linearity, RSD criteria—and aligns with practices discussed in ICH Q2(R1) and Q14

Future Directions

1. Addition of new solvents

As new toxicological data emerge, ICH may further expand PDE tables and reclassify solvents.

2. Automation in microextraction

Enhancing throughput through automated microextraction workflows could facilitate adoption in high-throughput QC labs.

3. Integration with green chemistry

Solvent selection strategies in early development are increasingly aligned with environmental, toxicity, and regulatory considerations.

4. Regulatory adoption lags

Continued cross-pharmacopeial convergence is expected but may take years for full implementation.

Conclusion

Recent advancements in residual solvent control highlight a mature regulatory environment supported by improved analytical methodologies and evolving toxicological understanding. Updates to the ICH Q3C guideline, combined with innovations in headspace gas chromatography and green chemistry practices, have strengthened patient safety while enhancing manufacturing efficiency. Ongoing regulatory alignment and methodological refinement will remain central to effective residual solvent management in pharmaceutical products**.**

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