Review Article

A Review: Residual Solvents and Various Effective Gas Chromatographic Techniques in the Analysis of Residual Solvent

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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 limit of residual solvents and to discuss various Gas Chromatographic (GC) techniques to analyze about all the residual solvents mentioned in ICH guideline, Q3C. Gas Chromatography is coupled with various other techniques to increase the sensitivity of the method. Various 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 to some drugs or pharmaceutical preparations are also covered under the study.

Keywords: Carrier gas, gas chromatography, headspace, residual solvents

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INTRODUCTION

Residual Solvents

According to USP residual solvents are organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. These are not completely removed by practical manufacturing techniques [1]. Since there is no therapeutic benefit from residual solvents, all of these should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements [2]. Over 60 residual solvents are included in USP. Testing for residual solvents in raw materials may be highly recommended as this solvent may be carried through the process and remain in the finished product. Early in the process, control is usually more cost-effective compared to remediation or even rejection of final product [1].

Regulation of Residual Solvents testing

Since the late 1970s, different investigations were done for the control of residual solvents. In 1997, limit contents for residual solvents in relation to their permitted daily exposure (PDE) were

issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in guideline Q3C [3]. ICH classified solvents in three categories and set limits depending on toxicity data for each solvent; Class I solvents (Solvents to be avoided), Class II solvents (Solvents to be limited) and Class III solvents (Solvents with low toxic potential) [2].

Different manufacturers produce the same pharmaceutical products using different organic solvents. Therefore, analysis of residual solvents becomes a challenging analytical task in pharmaceutical analysis and control. Unknown residual solvents are frequently detected during routine quality control testing. An error may occur while using existing official methods for their determination. Hence, we need to develop a rapid, sensitive method which identify, and quantitate all residual solvents in pharmaceuticals [4].

Methods for Establishing Exposure Limits

Options for describing Limits of Class II Solvents

Two options are available when setting limits for Class 2 solvents.

Option 1: The concentration limits in ppm stated in Table 2 can be used. They were calculated using following equation by assuming a product mass of 10g administered daily.

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

Here, PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances, excipients, or products. Therefore this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10g. Products that are administered in doses greater than 10g per day should be considered under Option 2 [2].

Option 2: It is not considered necessary for each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in (**Table 2**) can be used with the known maximum daily dose and equation above to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum [2].

Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. If Class I solvents are likely to be present, they should be identified and quantified. If solvents of Class II are present at greater than their Option 1 limits, they should be identified and quantified. If only Class III solvents are present, a non-specific method such as loss on drying may be used [2].

Residual Solvents types and limits [2]

They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class I Solvents: Solvents to be avoided

- Known human carcinogens
- Strongly suspected human carcinogens
- Environmental hazards
- The concentration limits of these solvents in Pharmaceutical products is usually between 2-8 ppm, except 1,1,1-Trichloroethane (1500ppm) which is a environmental hazard

Class II Solvents: Solvents to be limited

- Non-genotoxic animal carcinogens
- Irreversible toxicity such as neurotoxin-city or teratogenicity.
- Solvents suspected of other significant but reversible toxicities
- The concentration limits of these solvents are in the range of 50-3880 ppm

Class III Solvents: Solvents with low toxic potential

- Solvents with low toxic potential to man
- No health-based exposure limit is needed
- The concentration limits of these solvents are 5000 ppm

Limits: Drug products should contain no higher levels of residual solvents than can be supported by safety data.

Class I Residual Solvents

Table 1: Restricted Limits of Class I Residual Solvents

Solvent	Concentration limit
Benzene	2
Carbon Tetrachloride	4
1, 2- Dichloroethane	5
1, 1- Dichloroethene	8
1,1,1- Trichloroethane	1500

Class II Residual Solvents

Table 2: Restricted limits of Class II residual solvents

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene	21.7	2170

Class III Residual Solvents

The concentration limits of 5000 ppm would be acceptable for these solvents as these solvents are less toxic and of lower risk to human health.

Table 3: List of Class III Residual Solvents

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1 – Butanol	Methyl acetate
2 – Butanol	3 – Methyl -1- butanol
Butyl Acetate	Methylethylketone
tert- Butylmethyl Ether	Methylisobutylketone
Cumene	2 –Methyl-1- propanol

Dimethyl Sulphoxide(DMSO)	Pentane
Ethanol	1- Pentanol
Ethyl acetate	1- Propanol
Ethyl ether	2- Propanol
Ethyl formate	Propyl acetate
Formic acid	Tetrahydrofuran

Table 4: Non-Toxic Residual Solvents

1,1- Diethoxypropane	Methylisopropyl Ketone
1,1- Dimetoxypropane	Methyltetrahydrofuran
2,2- Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropylether	Triflouroacetic acid

Non-Toxic Residual Solvents

These classes of solvents are those for which, no adequate toxicological data was found.

Methods for Residual Solvent Analysis [5]

Measuring the weight loss of a sample during heating **(Loss on drying)** is a very old and a simple method for determining the content of volatile residues. But it is totally a non-specific method and needs several grams of product to achieve a detection limit of about 0.1%. Moreover, atmospheric humidity can significantly modify the results obtained by the loss of weight method.

Infrared spectroscopy **(IR)** and Fourier Transform Infrared Spectrometry **(FTIR)** are used to determine residual Tetrahydrofuran, Dichloroethane and Methylene Chloride in polymer samples by measuring the characteristic solvent bands in the spectra. The most common limiting factors is the high detection limit (above 100 ppm) and a lack of accuracy at low concentrations.

Thermogravimetric Analysis (TGA) is used to measure the concentration below 100ppm using only a few milligrams of substance. **Differential Thermal Analysis (DTA)** or **Differential Scanning Colorimetry (DSC)**, are more sophisticated methods which can be used for the determination of residual solvents. Nowadays all of above methods are replaced by **Gas Chromatography (GC)** as it has excellent separation ability, and can detect residual solvent up to a very low detection limits (up to ppb).

Gas Chromatography in detection of Residual Solvents: a Fast and Sensitive Technique

Gas Chromatography is a natural choice for residual solvents which have relatively low boiling points and are generally thermally stable. However, different aspects like injection systems, columns, and detectors are considered for the better results. Selection of appropriate systems, results in shorter time of analysis and lower detection limits [5].

The choice of injection system is determined by the sample type, the types of analytes, their quantity levels and available lab equipment.

1) Direct Injection

The direct injection technique can be employed when the tested sample is soluble in organic solvents (dissolution media) which have low boiling and all other components of sample also evaporate at relatively low temperature. This method is more time consuming method than headspace chromatography [5].

2) Headspace

The headspace analysis, is an extraction technique for semi volatile and volatile compounds, and generally can be divided into two forms: static and dynamic [5].

- **Static headspace sampling**
  A liquid or solid sample is placed in a vial and heated. Then a single aliquot of gas is collected over sample and transferred to gas chromatography. A gas sample is collected after the equilibration between

gas and liquid (or solid) phase is reached. It has been a primary tool for analysis of volatile organic compounds in environment, flavors and fragrance analysis for decades [6].

- **Dynamic headspace sampling**
  In dynamic headspace sampling carrier gas is passed through a liquid sample, and then volatile analytes are trapped on a sorbent and desorption onto a gas chromatography. This is a well- known and validated technique. It is the method of choice for analysis of extremely low (ppb and ppt) concentrations of volatile organic compounds in aqueous matrices [6].

Headspace gas chromatography (HSGC) is a very useful tool for the analysis of trace compounds that cannot injected with syringe or have many difficulties if injected with a syringe. It is an automated instrument which is useful for routine work and also eliminate problem related to contamination and sample carry over [7]. Even non-volatile organic solvents can be detected using HSGC method. In this method organic acids are methylated and converted to volatile methyl esters or dimethyl ester in a headspace vial and injected by the auto sampler [8].

The carrier gas choice can influence the analysis speed. An optimal temperature-program rate gives the best separation in the least time and can also influence analysis speed. Isothermal analyses provide the fastest overall analysis times for simple mixtures of solutes with similar volatilities in hyponated techniques [9].

Analysis of Residual Solvents

Analysis of Class I Residual Solvents

Headspace Gas Chromatography (HSGC) equipped with a programmed temperature vaporizer (PTV) and a mass spectroscopic (MS) detector is used for the detection of class I residual solvents.

Solvent vent injection system

The injector start temperature is adjusted to 5ºC and vent flow is adjusted to 50.0 ml/min. After about 2 minutes, the split valve is closed. The temperature is then raised to 250ºC with a liner flash-heated of 12ºC/sec. The analytes are then transferred from the liner to the capillary column. The split valve is then opened. The liner temperature is held at 250ºC for 8.00 min.

Gas Chromatography

Table 5: Gas Chromatographic Conditions for Analysis of Class I Solvents

Instrument used	Agilent 6890 GC
Column	DB-VRX capillary column (20m × 0.18mm × 1µm)
Column oven temperature program	Initial temperature of 35ºC for 4.50 min, then raised at a rate of 20ºC/min to 70ºC, then increased at 70ºC/min to 175ºC, and then further increased at 45ºC/min to 240ºC and held for 1.0 min

Mass Spectrometry

Quadrupole mass spectrometer (HP 5973 N) is used as the detector. It is operated in the electron impact mode using 70eV ionization voltage. The ion source temperature is 230ºC and the quadrupole is set to 150ºC. It is a novel and very sensitive method for the fast screening and determination of 1, 1-Dichloroethene, 1, 2-Dichloroethane, 1, 1, 1-Trichloroethane, Carbon tetrachloride and Benzene (class 1 solvents) in pharmaceutical products. The limits of detection ranged from 4.9 ppt (Benzene) to 7.9 ppt (1, 2-Dichloroethane) and precision is equal to or lower than 12% in all the cases of class one residual solvent. This method achieves an improvement in sensitivity with respect to conventional headspace methods due to the use of the PTV [10].

Analysis of Classes I and II Residual Solvents

Flow- modulation technique can be used to increase the speed gas chromatographic (GC) separation of residual solvents.

Instrument used for the analysis is Agilent 6890 GC equipped with electronic inlet pressure control and flame ionization

detection (FID). Two columns used are Rtx-Stabilwax, 15m × 0.25mm (Polyethylene Glycol stationary phase) and Rtx-200, 30m × 0.25mm (Trifluoropropylmethy-lpolysiloxane). The columns are joined to each other using a four-port Gerstel Graphpack. The volatile compounds are separated on a series-coupled column (dual column system) one of which is a Polyethylene Glycol column and another one is Trifluoropropylmethyl or dimethylpolysiloxane column. A valve between the junction point of the dual column and a source of carrier gas is opened for intervals of 2-8sec. This stops or slightly reverses the flow of carrier gas in the first column. Stop-flow pulses are used to increase the separation of target analytes that overlap in the total chromatogram, compared to non-stop-flow.

36 compounds based on ICH Classes I and II residual solvent lists, are resolved in 12 min using the stop-flow technique and a single chromatographic analysis. These residual solvents are 2-Methylpentane, Hexane, Methylcyclopentane, 1,1-Dichloroethene, Methylcyclohexane, trans-1,2-Dichloro-ethene, Carbon tetrachloride, 1,1,1-Trichloroethane, Methanol, 1,2-Dimethoxy-ethane, 1,1-Dichloromethane, Benzene, cis-1,2-Dichloroethene, Trichloroethene, Aceto-nitrile, Chloroform, Toluene, 1,4-Dioxane, 1,2-Dichloroethane, 2-Hexanone, p-Xylene, m-Xylene, Nitro-methane, 2-Methoxy-ethanol, Pyridine, o-Xylene, Chlorobenzene, 2-Ethoxyethanol, 1,1,2-Trichloroethane, N, N-Dimethylacet-amide, 1,2,3,4-Tetrahydro-naphthalene, Ethylene glycol, 1-Methyl-2-pyrrolidinone, Dimethylformamide, Form-amide and Sulfolone.

The method is more effective as it uses columns of different polarity and hence separation of polar components and non-polar components in a pharmaceutical product can do at the same time. This system is operated in stop-flow mode to increases the separation and hence for the better sensitivity [11].

Analysis of Class I, Class II and Class III Residual Solvents

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 150ºC, detector 290ºC, oven initial temperature 40ºC maintained for 4 min, then raised at a rate of 10ºC/min to 160ºC, 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 classes I solvents, 17 class II solvents, 17 class III solvents and three unclassified solvents according to ICH guideline Q3C. these are; Benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane, Acetonitrile, Chloro-benzene, Chloroform, Cyclohexane, 1,2-Dichloroethene, Dichloromethane, 1,2-Dimethoxyethane, N,N-Dimethylacetamide, N,N-Dimethylformamide, 1,4-Dioxane, 2-Ethoxyethanol, Hexane, Methanol, 2-Methoxyethanol, Methylbutyl ketone, Methylcyclohexane, Nitromethane, Pyridine, Tetrahydrofuran, Tetralin, Toluene, 1,1,2-Trichloroethene, Xylene, Acetone, 1-Butanol, 2-Butanol, Butyl acetate, tert-Butylmethyl ether, Dimethyl sulfoxide, Ethanol, Ethyl acetate, Ethyl ether, Heptane, Isobutyl acetate, Isopropyl acetate, Methyl acetate, 3-Methyl-1-butanol, Methylethyl ketone, Methylisobutyl ketone, 2-Methyl-1-propanol, 1-Pentanol, 1-Propanol, 2-Propanol, tert-Butanol, Isopropyl ether and Isooctane.

This method successively been used, with only minor modifications, for many drug substances during development. Quan-tification 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 [12].

Analysis of Class II and Class III Residual Solvents

For the determination of class II and class III residual solvents in drug substance a generic static headspace gas chromatog-raphy method is used.

Gas chromatography

Table 6: Gas Chromatographic Conditions for Analysis of Class II and Class III Solvents

Instrument used	Agilent 6890A GC equipped with an FID and a 7694 HS sampler
Column	Agilent DB-624 (6%cyanopropylphenyl & 94% dimtheylpolysiloxane) fused silica capillary column, (30m × 0.32mm×1.8µm)
Column oven temperature program	35ºC (Hold 0-3 min), raised to 110ºC at 4ºC/min, (Hold 3-21.75 min), raised to 240ºC at 40ºC/min (Hold 21.75-25 min), at 240ºC (Hold at 25-30 min)
Inlet temperature	200ºC
Inlet split ratio	1:1
Carrier gas	Helium

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 method is useful for the analysis of Methanol, Pentane, Ethanol, Ethyl ether, Acetone, Ethyl formate, 2-Propanol, Acetanitrile, Methyl acetate, Dichloromethane, 1,2-Dichloroethene, Methyl tert-butyl ether, n-Hexane, 1-Propanol, Nitromethane, 1,2-Dichloroethene, Methylethyl ketone, Ethyl acetate , 2-Butanol, Tetrahydrofuran, Chloroform, Cyclohexane, 2-Methyl-2-butanol, 1,2-Dimethoxyethane, 2 Methyl-1-propanol, 2-Methoxyethanol, Isopropyl acetate, n-Heptane, 1,1,2-Trichloroethylene, 1-Butanol, Methylcyclohexane, 1,4-Dioxane, Propyl acetate, 2-Ethoxyethanol, 4-Methyl-2-pentanone, Pyridine, 3-Methyl-1-butanol, Toluene, Isobutyl acetate, 1-Pentanol, 2-Hexanone, Butyl acetate, Chlorobenzene and p-Xylene.

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 150ºC (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 [13].

A Fast Gas Chromatography analysis of Class II and Class III Residual Solvents

Fast separation of residual solvents can be achieved using 10m × 0.1mm × 0.4µm DB-624 (bonded 6% Cyanopropylphenyl–94% Dimethylpolysiloxane) capillary GC column which have a single analysis time less than 4.9 min which can be shortened to less than 1.5 min using combined temperature and pressure programming. Solvent used for dilution is DMSO.

Gas Chromatography

Table 7: Gas Chromatographic Conditions for Analysis of Class II and Class III Solvents

Instrument used	Agilent 6890A GC equipped with an FID and headspace
Column	DB-624 (10m × 0.1mm × 0.4µm) capillary GC column
Column oven temperature program	35ºC for 0.69 min, then raised at a rate 20ºC/min to 90ºC, then raised at a rate 50ºC/min to 180ºC and held for 1 min.
Inlet temperature	140ºC
Inlet split ratio	1:120
Injection volume	0.2 µl
Carrier gas	Helium

About 40 commonly used solvents are analyzed using this method. The solvents that can be analyzed are Methanol, Pentane, Ethanol, Diethyl ether, Acetone, 2-Propanol, Methyl acetate, Acetonitrile, Methylene chloride, tert.-Butanol, Methyl tert.-butyl ether, n-Hexane, Isopropyl ether, 1-Propanol, Nitromethane, Methyl ethyl ketone, Ethyl acetate, Tetrahydrofuran, Chloroform, 1,1,1-Trichloroethane, Cyclohexane, Carbon tetrachloride, 2-Methyl-1-propanol, Benzene, 1,2-Dichloroethane, Methoxyethanol, Isopropyl acetate, n-Heptane, n-Butanol, Methylcyclohexane, 1,4-Dioxane, Methyl isobutyl ketone, Pyridine, 3-Methyl-1-butanol, Toluene, 1-Pentanol, n-Butyl acetate, Dimethylformamide, m-Xylene, p-Xylene, o-Xylene and Dimethyl sulfoxide. Advantage of this method is that a fast separation of 40 commonly used, ICH class II and class III solvents can be achieved in a single analysis in less than 4.9 min [14].

A simple HSGC analysis of Residual Solvent

There is an automated headspace GC method, which is used for the analysis of eight common process solvents and the five solvents whose quantification is required by the US Pharmacopeia. Dimethyl formamide is used as diluting solvent. The equilibrium headspace gas formed at 60°C is analyzed using a megabore capillary column. Quantification is performed by the standard addition technique to eliminate any possibility of matrix effects. This method is very sensitive, precised, accurate and linear.

The column used for method is Nukol, acid-modified, bonded Polyethylene Glycol capillary column (60 mm × 0.53mm I.D. × 0.50µm) for chromatographic separation of the solvents. The carrier gas used is Helium with a total flow-rate of 4.2 ml/mm. This technique uses the headspace auto sampler. Injections are made in the splitless mode through a packed-column [15].

HSGC analysis of Residual Solvents by using EC-5 Column

Using EC-5 column in gas chromatographic method simultaneous analysis of sixteen residual solvents can be done. The selection of the columns is proposed through matching of polarities of solutes with stationary phases. EC-5 column contains 5% Phenyl and 95% Dimethylpolysiloxane as the stationary phase. EC-5 column (30m x 0.53mm x 0.25µm) is used in this method. Shimadzu 17A, used for the development of GC methods using headspace mode of injection.

This method shows good separation and resolution between the peaks of the sixteen solvents. The retention time recorded as following for different solvents: Methanol 1.40 min, Ethanol 1.66 min, Dichloromethane 1.90 min, Acetone 2.94 min, Tetrahydrofuran 3.37 min, Hexane 3.63min, Ethyl acetate 4.34 min, Isopropyl alcohol 4.97 min, Acetonitrile 5.68 min, Heptane 5.75 min, 1, 4-Dioxane 6.19 min, Toluene 9.19 min, Pyridine 10.85 min, Butyl acetate 12.69 min, Xylene 13.03 min and N, N- dimethyl formamide 14.11 min. The resolution for headspace injection method is calculated between the peaks of methanol and Ethanol as 2.58, Ethanol and Dichloromethane as 1.69, Dichloromethane and Acetone as 6.84, Acetone and tetrahydrofuran as 2.84, Tetrahydrofuran and Hexane as 1.32, Hexane and Ethyl acetate as 1.16, Ethyl acetate and Isopropyl alcohol as 6.36, Isopropyl alcohol and Acetonitrile as 4.70, Acetonitrile and Heptane as 1.48, Heptane and 1,4-Dioxane as 2.94, 1,4-Dioxane and Toluene as 7.96, Toluene and Pyridine as 10.36, Pyridine and Butyl acetate as 12.32, Butyl acetate and Xylene as 3.33 and Xylene and N,N-dimethyl formamide as 7.22.

This is a simple gas chromatographic method for the simultaneous estimation of residual solvents in drug substances and drug products. This method is highly specific, accurate, precise and rugged [16].

A Solid-Phase Microextraction - HSGC method for the determination of Residual Solvents

Solid-phase microextraction coupled with gas chromatography could be used for the determination and quantification of residual solvents in drugs. Four solvents used for the experiments are Ethanol, Cyclohexane, Triethylamine and Pyridine. The most sensitive results found using a Carboxen-polydimethylsiloxane fiber in the headspace of the aqueous solution that contained the dissolved powder. A good

extraction of Ttriethylamine is obtained by adding a concentrated phosphate buffer to the aqueous solution to set the pH at 9.6. Standard additions method is used for quantitative analysis.

Five types of fiber used for the experimentation;

- Polydimethylsiloxane (PDMS) 100 mm
- Polydi-methylsiloxane-divinylbenzene (PDMS–DVB) 65 mm
- Carbowax-divinylbenzene (CW-DVB) 65 mm
- Polyacrylate (PA) 85 mm
- Carboxen-polydi-methylsiloxane (CAR-PDMS) 75 mm.

Due to high volatility of the solvent analyzed and long desorption time no significant fiber carry-over is observed.

Instrument used for analysis is Varian 3800 CX system connected to Varian 8200 CX Auto sampler for SPME. GC is equipped with a flame ionization detection (FID) system. The injector temperature is 300ºC. It worked in splitless mode for 1 min and then a split ratio of 1:40 is applied for the rest of the analysis. Detector temperature is 270ºC with a flow rate of hydrogen 30 ml/min and air 300 ml/min. Carrier gas used is Helium. The column used to achieve separation is 624 CB columns (30m × 0.25 mm ID × 1.8 µm). This method can detect solvents to a ppb level and the method is accurate and linear. SPME-GC is an elegant alternative for the determination and quantitation of residual solvents. This SPME-GC can be used in the pharmaceutical industry for solvent residue determination. SPME-GC should be evaluated for other kinds of pharmaceutical formulations, such as creams, patches or suppositories etc. [17].

Other Methods

For a better performance of gas chromatography, parallel dual column system is used for quantification of residual solvents in pharmaceuticals. Two columns of different polarities, SPB1 and HP-INNOWAX, are connected with a 'Y' splitter, constituted this dual pathways system. About fifty-two solvents can be analyzed by using this system. This method is validated according to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Through a single run, preliminary identification and quantification can be performed by using this method [4].

The solvation parameter model can be used to develop of a method for the analysis of residual solvents in pharmaceuticals. The solvation parameter model has been successfully applied in the study of column selectivity in gas chromatography. The retention times of the organic solvents on these columns could be predicted using the established solvation parameter models. The predicted retention times helped in column selection and in optimizing chromatographic conditions during method development [18].

1-n-Butyl-3-methylimidazolium dimethyl phosphate (BMIM DMP) is one of the most suitable ionic liquid as solvent for the headspace gas chromatographic analysis of solvents with very low vapor pressure such as dimethylsulfoxide, N-methylpyrrolidone, sulfolane, tetralin, and ethylene glycol [19]. Using new solvent room temperature ionic liquid matrix media, testing of residual solvents in pharmaceutical preparations with static headspace gas chromatographic (SH-GC), gives better sensitivities for the residual solvents [20]. Matrix medium such as Dimethylsulfoxide (DMSO), N,N-dimethy-formamide (DMF), N,N-dimethylacetamide (DMA), Benzyl alcohol, 1,3-Dimethyl-2-imidazolidinone and water may be used for the determination of residual solvents in pharmaceuticals by static headspace gas chromatography [21].

A generic static headspace-gas chromato-graphy analysis method is proved to be suitable for the majority of samples and residual solvents. But this method lack sensitivity for some high boiling point residual solvents such as N, N-dimethyl-formamide, N-dimethylacetamide, dimethyl sulfoxide and benzyl alcohol. For those solvents liquid paraffin is used as new dilution medium for the analysis of these residual solvents [22].

A multiple headspace single-drop micro-extraction (MHS-SDME) eliminates the matrix effect on the quantitative analysis of solid samples and is based on extrapolation to an exhaustive extraction of consecutive extractions from the same sample. MHS-

SDME has a great potential for the quantitative determination of residual solvents directly from the solid drug products due to its low cost, ease of operation, sensitivity, reliability and environmental protection [23].

The results of quantitative gas chromatography-mass spectrometry can be improved using electron ionization beam as a modified ion source [24]. GC-MS-SPME is a much sensitive and more precised method of determination of residual solvents [25]. For analysis of residual solvents in pharmaceuticals gas chromatograph-mass spectrometry (GC-MS) and gas chromatograph-Fourier transform infrared spectrometry (GC-FTIR) are very sensitive and accurate techniques [26]. Thermal desorption-Gas chromatography/mass spectrometry (TD-GC/MS) is a novel method for the determination of residual solvents. This method does not require any sample pretreatment and uses only a very small amount of sample [27].

Evaluation of some Pharmaceutical Formulations

Residual Solvents analysis in some Antibiotics: Evaluation of the European Pharmacopoeia method

The International Conference on Harmonization (ICH) limits the amount of residual solvent in pharmaceuticals. The European Pharmacopoeia (Ph. Eur.) also limits the amount of residual solvents. Water insoluble samples may be analyzed using Dimethyl formamide as dilution solvent at high equilibration temperatures such as 105ºC. Water insoluble and temperature sensitive drugs create problem by this method especially antibiotics. Antibiotics are complex in nature and show several other volatile impurity peaks in the chromatogram besides the residual solvent. An alternative dilution medium is used (DMSO-water) for the evaluation of residual solvent in antibiotics, which offers optimum sensitivity while working at lower equilibration temperatures such as 80ºC. 70 commercial bulk antibiotic samples from different origin were investigated. These antibiotics were of different categories; erythromycin (23), doxycycline (12), gentamicin (12), colistin (9), cefalexin (3), cefradine (3), cefadroxil (1), gramicidin (3), tetracycline (1), ampicillin trihydrate (2) and amoxicillin trihydrate (2).

HS-GC-FID The GC-FID (DELSI 200 capillary gas chromatograph) connected with a static headspace auto sampler is used. The headspace sampler is equipped with a 1ml injection loop.

HS-GC-MS The GC instrument (Auto system XL capillary gas chromatograph) is coupled to a Turbomass mass spectrometer (PerkinElmer). The headspace used is a Turbomatrix (PerkinElmer). The column used for the separation is an AT-Aquawax (30m × 0.53mm × 0.5µm). Stationary phase used is PEG. PEG offers more stability towards repeated injections of water. The carrier gas used in experiment is Helium.

Application of MS is found mandatory for the identification of individual solvent. To reduce the possibility of carryover of high boiling point analytes needle and transfer line temperature are increased (105ºC and 120ºC, respectively). Sensitivity is enhanced by alternative dilution medium, a mixture of organic solvent with water [28].

Static HSGC method for determination of Residual Solvents in the Antibiotic L-749,345

An automated static headspace gas chromatographic method is used for the determination of residual solvents in the antibiotic L-749,345. Quantitation is performed using external standard method. The gas chromatography and headspace injector method parameters chosen for determination of trace levels of Methylene chloride in the presence of Methanol, Ethanol and n-Propanol.

Gas chromatography apparatus used for headspace chromatography is Perkin Elmer headspace gas chromatograph equipped with a flame ionization detector. DB-1 fused-silica column (0.32mm × 30m × 5.0µm) is used as column. GC temperature program is 35ºC isothermal for 8 min, then raised at a rate 25ºC/min to 125ºC. The injector temperature is 180ºC. Split ratio is 25:1. FID detector temperature is 250ºC. Carrier gas used in experimentation is Helium. The headspace GC residual solvent method for L-749,345 effectively eliminated the column degradation problem encountered with the direct injection GC method. The method is much accurate and

rugged. By using this method, column lifetime is increased and the run time is reduced [29].

Dynamic HSGC method for determination of Residual Solvents in Biodegradable Microparticles

Residual solvents in biodegradable microparticles are analyzed by developing a new sensitive and reliable method.

This method can be described in two steps:

- The purge and trap procedure in which an extraction process of a liquid phase with an inert gas flow is carried out. It results in enrichment of the extracted volatiles on a connected sorbent tube. This enrichment is due to an adsorptive process and allows the determination of trace amounts of organic volatiles. The headspace vial containing the aqueous sodium hydroxide, the hydrolyzed microparticles, the internal standard and the residual solvent is positioned and incubated in the stripping device. Nitrogen as inert gas is bubbled through the solution in a defined volume. The gas flow passes a sampling tube filled with a solid sorbent into which volatiles are trapped and enriched by adsorption.
- Thermal desorption of the sampling tube after connection with the desorption unit of the gas chromatograph is the next step. During this step the desorbed compounds are again pre concentrated in a cold trap cooled with liquid nitrogen in front of the capillary column. The fast heating up of the cold trap accompanied by the start of the gas chromatography system results in a very small starting peak width which allows optimum utilization of the separation efficiency of the capillary column.

GC analysis apparatus used is Hewlett Packard 5880 equipped with FID. Carrier gas used is Helium with a flow rate of 1.2 ml/min. The column used is Chrompack Capillary column (25m long and 0.32mm diameter). The applied method is optimized for methylene chloride with regard to precision, linearity, purge and trap conditions and stability of the internal standard. This dynamic headspace gas chromatography method is appropriate to determine the residual solvent in biodegradable microparticles [30].

GC method for analysis of Residual Solvent in Radiopharmaceutical Formulations containing up to 12% Ethanol

Radiopharmaceuticals for human applications are dissolved in isotonic, sterile and pyrogen-free solutions. These solutions can contain up to 12% Ethanol, depending on the production method employed. Possible residual solvents need to be analyzed before the application of these radiopharmaceutical formulations in human subjects. A new analysis method is used for the detection and quantitation of residual solvents in radiopharmaceutical solutions for human applications. This method is especially suitable for the fast quantitative analysis of residual solvents in radiopharmaceutical formulations where 5-12% Ethanol is present. This method uses a simple direct gas chromatography injection technique where no special sample treatments or special injection techniques (like head-space or solid-phase microextraction) are necessary. In Radiopharmaceuticals Acetone, Acetonitrile, Dichloromethane, Diethyl ether, DMSO, Ethanol, Diisopropylamine, Diisopropylethylamine, N, N-Dimethylformamide, Tetrahydrofolate, Triethylamine and Methanol are analyzed as residual solvent using this method. Gas chromatography is performed using Interscience Trace Gas Chromatograph, equipped with a splitless packed column injector and a flame ionization detector (FID). The method uses the Rt-1000 (2.4m × 2-mm) column.

This method meets the requirements of the ICH or United States Pharmacopeia for the detection and quantitation of residual solvents the method is accurate and linear. The advantage of the method is that quantitation limit is in the lower parts-per-million range, which is sufficient given the need for a fast analysis and the maximally allowed concentration for these residual solvents [31].

HSGC-SPME-MS method for analysis of Residual Solvent trapped into illicit Cocaine

Solvent analysis of the residues that are trapped into crystals of illicit drugs provides useful evidence for monitoring

current use trend in the chemical underground. This analysis is a useful tool to achieve the complete chemical characterization of street drugs for comparative examination of separate specimens. A HSGC-SPME-MS method is used in order to perform simultaneous qualitative and quantitative analysis of solvent residues in cocaine samples. In this method Gas chromatography-Mass spectrometry is used for the analysis of residual solvents after their extraction from drug matrices by solid-phase microextraction (SPME) in static head space. Quantitative analysis is carried only for the solvents identified at concentration values higher than 1ppm. Quantitative profile of the solvents trapped into illicit cocaine can be used as a suitable tool to investigate the kind of solvent involved during the clandestine manufacturing of the drug.

The SPME device used is Supelco. Fiber used is 100mm Polymethylsiloxane-coated fiber. Gas chromatograph used is Hewlett-Packard5890 gas chromatograph. The column used for separation is capillary HP1301 column (60m × 30.25mm). The gas chromatograph is coupled with a Hewlett-Packard5889 mass detector (electronic impact 70eV).

This method is used to detect residues of solvents in 47 illicit street cocaine samples like Methanol, Ethanol, Pentane, Diethyl ether, 2-Propanol, Acetone, Methyl pentane, Dichloromethane, Hexane, 2-Butanone, Methyl cyclopentane, Ethyl acetate, Chloroform, Cyclohexane, Acetic acid methyl ester, Benzene, n-Propyl acetate, Methyl cyclohexane, Methyl isobutyl ketone, Toluene, Ethyl benzene, 1,3-Dimethyl benzene, 2-Butoxyethanol, Decane, 1,2,3-Trimethyl benzene, Undecane, Acetophenone and 2-Butoxy ethylacetate [32].

Static HSGC method for analysis of the Residual Ethanol in Hydro alcoholic sealed Hard Gelatin Capsules

To quantitatively determine the residual ethanol which is used to seal the hard gelatin capsules by liquid encapsulated and micro spray sealing, there is a method using static headspace gas chromatography (HS-GC) with immiscible binary solvents. For gas chromatography HP6890 HS-GC is used which is equipped with a FID system. The column used is capillary column DB-ALC1 (30m × 0.32mm × 1.8µm). The carrier gas used is Helium.

This method is linear and accurate. The limit of quantitation is 5µg/mL. Aliphatic hydrocarbons of Decane, Dodecane and Heptane, which are immiscible with the capsule sample solutions, can be added into a headspace vial to significantly improve the sensitivity of the static HS-GC method by reducing the headspace volumes. It is observed that the Ethanol headspace concentrations can be increased by four folds when aliphatic hydrocarbon solvents are added into the aqueous sample solutions in a headspace vial. The increase of the Ethanol headspace responses is both due to significantly decrease of the partition coefficients of Ethanol in the air-water system and to the reduction of the headspace volumes by adding an aliphatic hydrocarbon into the aqueous sample solutions in a head space vial [33].

HSGC method for analysis of Residual Solvents in D-002 (new active ingredient from Beeswax)

D-002 is a natural active ingredient from beeswax which consists of a mixture of aliphatic saturated fatty alcohols, with antioxidant and anti-ulcer effects. In the process of obtaining the D-002, n-Hexane and Acetone are used, which are class 2 and 3 residual solvents respectively. Therefore it becomes necessary to have a validated analytic methodology. There is a method for simultaneous estimation of residual n-hexane and acetone in D-002 using the headspace gas chromatography (HS/GC). A gas chromatograph HRGC 4000B coupled to headspace and equipped with flame ionisation detector is used here. The column used is BP-1 wide bore column (30m × 0.53mm × 3.0µm) [34].

Residual Solvents analysis in Gel Extrusion module tablet formulations by Static HSGC

Controlled or sustained-release drug delivery systems are widely used to achieve desired therapeutic effects with the advantages of eliminating undesirable side effects, diminishing repeated dosages, and improving biological and pharmaceutical

efficiencies. Several organic solvents are used during the manufacture of gel extrusion module tablet formulation product e.g. Ethanol, Methanol, Isopropanol, and Acetone etc. Low levels of these organic solvents are remains in the drug product even after the drying process which necessitates the analysis of residual solvent in gel extrusion module tablet. A static headspace-gas chromatographic (SHS-GC) method is used for the quantitation of residual solvents in gel extrusion module tablet formulations. Quantitation is done using external standard analysis. The SHS-GC method is validated according to regulatory requirements.

Gas chromatography instrument used is Hewlett–Packard 6890 gas chromatograph equipped with headspace sampler, and a flame ionization detector (FID). Headspace auto sampler conditions are as follows; Oven temperature 85 °C, transfer line temperature 110 °C and loop temperature, 90 °C. Column used for chromatographic separation of the solvents is Rtx-1701 column (60m × 0.53 mm × 1.0µm). The carrier gas is Helium and Split ratio is 1:10.

This method is specific, sensitive, precise, and accurate. It is a simple and rapid method for the study residual solvents in complex pharmaceutical products. This method reduces routine maintenance of the GC system and provides much more accurate and precise quantitation results than the direct GC method [35].

GC-MS method for the analysis of Residual Solvents in Counterfeit Tablets and Capsules

A fast headspace Gas chromatography-Mass spectrometry **(**GC-MS) method is used for the detection and quantification of residual solvents in counterfeit tablets and capsules. The method is validated for 10 solvents, Ethanol, 2-Propanol, Acetone, Dichloromethane, Ethyl acetate, Chloroform, Carbon tetrachloride, Benzene, Toluene and Ethyl benzene. This method is used for the screening and quantification of residual solvents in counterfeit tablets and capsules.

GC-MS system used is Agilent 6890N gas chromatograph with headspace sampler coupled to Agilent 5973N mass selective detector. The oven temperature is programmed from 60ºC (held for 5 min) to 270ºC at 25ºC/min. 270ºC is held for 10 min. The column used for the separation of residual solvents is Phenomenex 624 capillary column (60m × 0.32mm × 1.8µm). For quantification and validation the mass spectrometer is operated in SIM mode. The total run time is 24 min.

This method is accurate, linear, and precised. Hence method is suitable for routine analysis of counterfeit tablets. This method is fast and sensitive. The method can be used in the risk evaluation of counterfeit tablets and capsules concerning the public health [36].

Analysis of Residual Solvents in Amlodipine Besylate by Gas Chromatography

For the determination of Residual solvents (n-Hexane, Methanol, Isopropyl Alcohol, Toluene, O-Xylene, DMF & Acetic acid) in Amoldipine besylate Gas chromatography methos is used.

The gas chromatography apparatus used is Perkin Elmer Clarus 500 equipped with FID detector. The column used for separation is DB-FFAP (30m × 0.53mm × 1.0 µm). The injection volume of samples taken is 1µl and split ratio of the injection is 1:10. The temperature maintained at the injector and detector is 220ºC and 260ºC respectively. Nitrogen is used as the carrier gas. The diluent used is Dimethyl Sulfoxide.

This method is simple, specific, accurate and precise. The amount of residual solvents present in the Amlodipine besylate is found to be within the ICH limits. The RTs observed for the Residual solvents n-Hexane 3.03, Methanol 6.20, Isopropyl Alcohol 6.87, Toluene, 10.27, O-Xylene 14.57, DMF17.49 and Acetic acid 19.54 [37].

Analysis of Residual Solvents in Omeprazole Pharmaceutical formula-tions by HS-GC with Flame Ionization Detector

Omeprazole is a potent reversible inhibitor of the gastric proton pump H+/K+-ATPase. For the residual solvent determination of Omeprazole formulation head space gas chromatography is used. Based on Good manufacturing practices, measuring residual solvents is mandatory for the

release testing of all active pharmaceutical ingredients.

Gas chromatography apparatus used is Shimadzu-GC-2010 with head-space auto sampler equipped to a flame-ionization detector. The column used for separation is DB-624 (30m × 0.53mm × 3.0 µm) and Split ratio is 1:10. Oven temperature is maintained at 40ºC for 5 min, and then raised at rate of 7ºC/min to 220ºC, maintained for 10 min. Total run time is 40 min. Carrier gas used is Nitrogen. This method quantifies Methanol, Acetone, Isopropyl alcohol (IPA), Methylene dichloride (MDC) and Toluene in concentrations from a few to a few percent [38].

Static HS-GC method for analysis of Low and High boiling Residual Solvents in Betamethasone Valerate

Betamethasone valerate is a steroid with anti-inflammatory properties and is used to manufacture dermatological drug products for topical applications. Both low boiling (Acetone and Methylene chloride) and high boiling (n-Butyl ether and Dimethylsulfoxide (DMSO)) solvents are used in the final steps of BV synthesis.

Gas chromatography apparatus used is Agilent 6890A GC equipped with an FID and headspace. Column used for separation is DB-624 (30m × 0.32mm × 1.0µm). Two alternate columns, SPB-624 or AT-624 can be used for the analysis.

This method is found to be accurate, linear, precise, reproducible, specific and robust for its intended purpose. Several other APIs (Loratadine and a few other corticosteroid compounds) can be analyzed using the conditions of this method to evaluate and assess the versatility of this method for the purpose of residual solvents analysis for a wide range of APIs. The results of this evaluation strongly indicates that this method can be readily used (with minor modifications) to determine both low and high boiling residual solvents present in a wide range of APIs [39].

CONCLUSION

In the analysis of residual solvents various techniques employed are 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). The sensitive and effective result is obtained using Gas Chromatography. Furthermore Gas Chromatography is made more sensitive by combining this technique to various other techniques such as Head Space Gas Chromatography(HSGC), Fast Gas Chromatography, Head Space Gas Chromatography coupled Flame-Ionisation Detector (HSGC-FID), Head Space Gas Chromatography-Mass Spectrometry (HSGC-MS), Flow-Modulation Technique for GC, Thermal Desorption-Headspace Gas Chromatography (TD-HSGC), Head Space 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 the residual solvents are analyzed by using various Gas Chromatographic techniques. Gas chromatography is an effective and sensitive tool in the determination of residual solvents in excipients, drugs or Pharmaceutical preparations.

REFERENCES

1. United States Pharmacopoeia (USP-NF XXIV), The Official compendia of Standards, Rockville MD, United States Pharmacopoeial convention Inc.; 1985: 467.
2. ICH Draft Guidelines on Impurities: Guideline for Residual solvents, Q3C, 2005: 95.
3. Otero Raquel, Carrera Guillem, Dulsat Joan Francesc, Fabregas Jose Luis, Static Headspace gas chromatographic method for quantitative determination of residual solvents in pharmaceutical drug substances according to European Pharmacopoeia requirements, Journal of Chromatography A, 2004; 1057: 193-201.
4. Liu Ying, Hu Chang-Qin, Preliminary identification and quantification of residual solvents in pharmaceuticals using the parallel dual-column system, Journal of Chromatography A, 2007; 1175: 259-66.
5. Grodowska Katarzyna, Parczewski Andrzej, Analytical methods for residual solvents determination in pharmaceutical products, Acta Poloniae Pharmaceutica- Drug Research, 2010; 67 (1): 13-26.
6. Snow H. Nicholas, Slack C. Gregory, Head-space analysis in modern Gas

chromatography, Trends in analytical chemistry; 2002; 21(9): 608-17.
7. Kolb B., Application of an automated Headspace gas chromatography for trace analysis by Gas chromatography, Journal of Chromatography, 1976; 122: 553-68.
8. Heitefuss Stefan, Heine Andreas, Seifert Horst, Detection of non-volatile organic acids by Head-space gas chromatography, Journal of Chromatography, 1990; 532: 374-8.
9. Klee S. Matthew, Blumberg M. Leonid, Theoretical and Practical aspects of fast Gas chromatography and method translation, Journal of Chromatographic Science, 2002; 40: 234-47.
10. Perez Pavon Jose Luis, Nogal Sanchez del Miguel, Fernandez Laespada M Esther, Analysis of class 1 residual solvents in pharmaceuticals using Headspace-programmed temperature vaporization-fast gas chromatography-mass spectrometry, Journal of Chromatography A, 2007; 1141: 123-30.
11. 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.
12. Klick Silke, Skold Agneta, Validation of a generic analytical procedure for determination of residual solvents in drug substances, Journal of Pharmaceutical and Biomedical Analysis, 2004; 36: 401-9.
13. 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.
14. Chen K. Ted, Phillips G. Joseph, Durr William, Analysis of residual solvents by fast Gas chromatography, Journal of Chromatography A, 1998; 811: 145-50.
15. Kumar Narendra, Gow G. John, Residual solvent analysis by Headspace gas chromatography, Journal of Chromatography A, 1994; 667: 235-40.
16. Puranik S.B., Sharath S, Sanjay Pai P.N, Headspace gas chromatography analysis of residual solvents by using EC-5 column, International Journal of Pharmaceutical Chemistry Research, 2012; 1 (1): 22-7.
17. Legrand Stephanie, Dugay Jose, 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. Liu Ying, Hu Chang-Qin, Application of the solvation parameter model in method development for analysis of residual solvents in pharmaceuticals, Journal of Chromatography A, 2009; 1216: 86-91.
19. Laus Gerhard, Andre Max, Bentivoglio Gino, Schottenberger Herwig, Ionic liquids as superior solvents for Headspace gas chromatography of residual solvents with very low vapor pressure, relevant for pharmaceutical final dosage forms, Journal of Chromatography A, 2009; 1216: 6020-3.
20. Liu Feng-hua, Jiang Ye, Room temperature ionic liquid as matrix medium for the determination of residual solvents in pharmaceuticals by static Headspace gas chromatography, Journal of Chromatography A, 2007; 1167: 116-9.
21. Urakami Koji, Higashi Atsuya, Umemoto Kazuichi, Godo Masayuki, Matrix media selection for the determination of residual solvents in pharmaceuticals by static Headspace gas chromatography, Journal of Chromatography A, 2004; 1057: 203-10.
22. Ward D. Autry, Chao Zheng, John Bugalama, Kris Wolfs, Jos Hoogmartens, Erwin Adams, Bochu Wang, Ann Van Schepdael, Liquid paraffin as new dilution medium for the analysis of high boiling point residual solvents with static Headspace gas chromatography, Journal of Pharmaceutical and Biomedical Analysis, 2011; 55: 1017-23.
23. Yu Yingjia, Chen Bin, Shen Cidan, Cai Yi, Xie Meifen, Zhou Wei, Chen Yile, Li Yan, Duan Gengli, Multiple Headspace single-drop microextraction coupled with gas chromatography for direct determination of residual solvents in solid drug product, Journal of Chromatography A, 2010; 1217: 5158-64.
24. Autry D Ward, Wolfs Kris, Hoogmartens Jos, Adams Erwin, Schepdael Van Ann, Improving quantitative Gas chromatography-electron ionization mass spectrometry results using a modified ion source: Demonstration for a pharmaceutical application, Journal of Chromatography A, 2011; 1218: 4034-8.
25. Camarasu C Costin, Mezei-Szuts Maria, Varga Bertok Gabor, Residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME, Journal of Pharmaceutical and Biomedical Analysis, 1998; 18: 623-38.
26. Liu Ying, Hu Chang-Qin, Establishment of a knowledge base for identification of residual solvents in pharmaceuticals, Analytica Chimica Acta, 2006; 575: 246-54.
27. Keiji Hashimoto, Koji Urakami, Yasuhiro fujiwara, Syunji Terada, Chuichi Watanabe,

Determination of residual solvents in pharmaceuticals by Thermal Desorption-GC/MS, Analytical Sciences, 2001; 17: 645-8.
28. Sitaramaraju Yarramraju, Riadi Adil, Autry D Ward, Wolfs Kris, Evaluation of the European Pharmacopoeia method for control of residual solvents in some antibiotics, Journal of Pharmaceutical and Biomedical Analysis, 2008; 48: 113-9.
29. Natishan K Theresa, Wu Yan, Residual solvents determination in the antibiotic L-749,345 by static Headspace gas chromatography, Journal of Chromatography A, 1998; 800: 275-81.
30. Ruchatz F, Kleinebudde P, Muller BW, Residual solvents in biodegradable microparticles: determination by a dynamic Headspace gas chromatographic method, International Journal of Pharmaceutics 1996; 142: 67-73.
31. Klok P Robert, Windhorst D Albert, Residual solvent analysis by Gas chromatography in radiopharmaceutical formulations containing up to 12% ethanol, Nuclear Medicine and Biology, 2006; 33: 935-8.
32. Chiarotti Marcello, Marsili Remo, Moreda-Pineiro Antonio, Gas chromatographic-mass spectrometric analysis of residual solvent trapped into illicit cocaine exhibits using Head-space solid-phase microextraction, Journal of Chromatography B, 2002; 772: 249-56.
33. Li Jingyi, Shao Shan, Solorzano Mauro, Allmaier J Gary, Kurtulik T Paul, Determination of the residual ethanol in hydroalcoholic sealed hard gelatin capsules by static headspace gas chromatography with immiscible binary solvents, Journal of Chromatography A, 2009; 1216: 3328-36.
34. Antolin Ernesto Mendez, Quinonez Balcinde Yaisme, Validation of an analytical method for quality control of residual solvents (*n*-hexane and acetone) in D-002: New active ingredient from beeswax, Journal of Pharmaceutical and Biomedical Analysis, 2008; 47: 646-50.
35. Li Zhong, Han Yieng-Hau, Martin P Gregory, Static headspace gas chromatographic analysis of the residual solvents in gel extrusion module tablet formulations, Journal of Pharmaceutical and Biomedical Analysis, 2002; 28: 673-82.
36. Deconinck E, Canfyn M, Sacre P Y, Baudewynsa S, Coursellea P, Beera De J O, A validated GC-MS method for the determination and quantification of residual solvents in counterfeit tablets and capsules, Journal of Pharmaceutical and Biomedical Analysis, 2012; 70: 64-70.
37. V Anil Kumar, G. Aravind, I Srikanth, A. Srinivasarao, Ch Dharma Raju, Novel analytical method development and validation for the determination of residual solvents in amlodipine besylate by Gas chromatography, Der Pharma Chemica, 2012; 4(6): 2228-38.
38. Battu Reddy Prasanna, Reddy M S, Residual Solvents Determination by HS-GC with flame ionization detector in Omeprazole pharmaceutical formulations, International Journal of PharmTech Research, 2009; 1(2): 230-34.
39. Somuramasami Jayalakshmi, Wei Yu-Chien, Soliman F Emad, Rustum M Abu, Static Headspace gas chromatographic method for the determination of low and high boiling residual solvents in Betamethasone valerate, Journal of Pharmaceutical and Biomedical Analysis, 2011; 54: 242-7.