A Review on – “Estimation of Residual Solvents by Different Analytical Methods”

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Received: 11-03-2021; Revised: 17-06-2021; Accepted: 24-06-2021; Published on: 15-07-2021.

ABSTRACT
Residual solvents are the unwanted substances (solvents) used or created throughout the manufacture of a excipients, drug or pharmaceutical formulation and don't seem to be utterly removed by sensible ways within the final finished product. These solvents may be harmful in nature. Therefore, analysis of residual solvents becomes a necessary tool for the standard management of prescribed drugs. The appropriate limits for these substances are given in ICH. Solvents are widely used during the manufacturing, purification and processing of pharmaceutical substances. The residues of these solvents must be removed to the extent possible, as they do not have any therapeutic effect but can cause undesirable effects in the consumers. These solvent residues concentration should not exceed the limits prescribed in the ICH guidelines. This present review work is emphasized on various techniques (Loss on drying, Thermogravimetric analysis, Near-IR spectroscopy).

Keywords: Residual solvents, ICH guidelines, analytical methods.

INTRODUCTION

For pharmacopeial purposes, Residual Solvents in pharmaceuticals are defined as the Organic volatile chemicals that are used in the manufacturing of drug substances, excipients, or dietary ingredients, or in the preparation of drug products and dietary supplement products appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield or determine characteristics such as crystal form, purity, and solubility.

Therefore, the solvent may sometimes be a critical element in the synthetic process and may not be completely removed by the manufacturing process. This is because residual solvents do not provide any therapeutic benefit and they should be removed to the possible extent to meet the safety based limits, ingredient and product specifications, good manufacturing practices, or other quality-based requirements. The objective of this is to define acceptable amounts of residual solvents in pharmaceutical drug products and dietary supplement products for the safety of the patient.

Tests for residual solvents don't seem to be typically mentioned in specific monographs because the solvents used could vary from one manufacturer to another; but, the bounds to be applied should fits those nominative. This provides procedures for the analysis of residual solvents, though different valid methodologies may additional demonstrate compliance with the outlined limits. The bounds laid out in this don’t apply on to excipients, drug substances, or dietary ingredients except wherever laid out in the individual monographs.

However, residual solvent levels gift in drug substances, excipients, associated dietary ingredients is also accustomed demonstrate compliance as an integral a part of the management strategy, thereby reducing or eliminating the necessity for analysis within the product. In on residual solvents in coating materials, colorants, flavors, capsules, and acquisition inks is mostly not required unless category one solvents area unit utilized in the manufacture of those elements.¹

Classification of Residual Solvents by Risk Assessment

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 (RS) 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.
Table 1: Classification of Residual Solvents and Their Assessments

<table>
<thead>
<tr>
<th>Residual Solvents Classes</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 (solvents to be avoided)</td>
<td>Known human carcinogen. Strongly suspected human carcinogen. Solvents particularly to have ozone depleting properties.</td>
</tr>
<tr>
<td>Class 2 (solvents to be limited)</td>
<td>Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.</td>
</tr>
<tr>
<td>Class 3 (solvents with low toxic potential)</td>
<td>Solvents with low toxic potential to humans; no health-based exposure limit is needed</td>
</tr>
</tbody>
</table>

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

1. Drug substance or dietary active ingredient
   - Potential solvent sources include their use or formation during the synthesis or purification of the drug substance; their presence in raw materials or reagents used in their synthesis; or degradation of the drug substance.

2. Excipients and/or dietary ingredient
   - Potential solvent sources include their use or formation during the manufacture or purification of excipients.

3. Formulation
   - Potential solvent sources are associated with their use or formation during the official product manufacturing process.

The potential presence of other solvents as impurities in the solvents used must be taken into consideration in the assessment of solvents LTBP. Because of the high toxicity of benzene and other Class 1 solvents, all likely sources of these solvents must be considered. For example, potential sources of benzene may include its presence as an impurity in a solvent used in the manufacturing process; its use in the manufacture of starting material; or its production as a reaction by-product. In the event that the user has insufficient information to complete a thorough assessment of the potential sources of residual solvents (or as an alternative to performing this assessment), solvent screening may be used. Pharmaceutical drug products and dietary supplement products should contain no higher levels of residual solvents than can be supported by safety data. Those solvents that show toxicity of special concern or carcinogenicity, and/or atmospheric ozone-depletion effects (Class 1) should be avoided in the production of drug substances, dietary supplement ingredients, excipients, pharmaceutical drug products, and dietary supplement products unless their use can be strongly justified in a risk-benefit assessment. Those solvents associated with less severe but still significant toxicity (Class 2) should be limited to protect patients from potential adverse effects. Whenever it is practicable, less toxic solvents (Class 3) should be used.$^2$

Limits of Residual Solvents

Class 1: Solvents to Be Avoided

Class 1 residual solvents should not be used in the manufacture of drug substances, excipients, dietary ingredients, or official products because of their unacceptable toxicities or deleterious environmental effects. However, if their use in order to produce an official product with a significant therapeutic advance is unavoidable, their levels should be restricted unless otherwise stated in the individual monograph. The solvent 1, 1-trichloroethane is included in Table because it is a severe environmental hazard. The stated limit of 1500 ppm is based on a review of safety data.

Table 2: Control Limits for Class 1 Residual Solvents in Official Products: Solvents to Be Avoided

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration Limit (PPM)</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2</td>
<td>Carcinogen</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>4</td>
<td>Toxic &amp; toxicologic hazard</td>
</tr>
<tr>
<td>1,2 dichloroethylene</td>
<td>5</td>
<td>Toxic</td>
</tr>
<tr>
<td>1,1 dichloroethene</td>
<td>8</td>
<td>Toxic</td>
</tr>
<tr>
<td>1,1,1 trichloroethane</td>
<td>1500</td>
<td>Environmental hazard</td>
</tr>
</tbody>
</table>

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. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm.

Table 3: Class 2 Residual Solvents in Official Products

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>4.1 410</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>3.6 360</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.6 60</td>
</tr>
<tr>
<td>Cumene</td>
<td>0.7 70</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>38.8 3880</td>
</tr>
<tr>
<td>1,2 dichloroethene</td>
<td>18.7 1870</td>
</tr>
<tr>
<td>1,2 dimethoxyethane</td>
<td>10 100</td>
</tr>
</tbody>
</table>
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.

**Table 4: Class 3 Residual Solvents in Official Products**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>Isobutyl acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>Isopropyl acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisole</td>
<td>Methyl acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-butanol</td>
<td>3- methyl-1-butanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-butanol</td>
<td>Methyl ethylketone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butyl acetate</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tert-butylmethyl ether</td>
<td>2-methyl-1-propanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Pentane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>1-pentanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>1-propanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl ether</td>
<td>2-propanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl formate</td>
<td>Propyl acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formic acid</td>
<td>Triethylamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heptane</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Class 3 includes no solvent known to be a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg/day or less of each solvent (corresponding to 5000 ppm or 0.5% w/w in Option 1) would be acceptable for each solvent without justification. Higher amounts may also be acceptable, provided that they are realistic in relation to manufacturing capability and good manufacturing practice. If a Class 3 solvent limit in an individual monograph is greater than 0.5%, that solvent residual should be identified and quantified.

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

The concentration limits in ppm stated in Table 3 for Class 2 solvents and the general requirement for Class 3 (5000 ppm, equivalent to 0.5% w/w) are used. The values for Class 2 solvents were calculated using the equation below by assuming a product weight of 10 g administered daily.

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

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.

4 Identification, Control, and Quantification of Residual Solvents

Class 1 and 2 Residual Solvents

This describes analytical procedures (Procedures A, B, and C) for evaluating the levels of all Class 1 and the majority of Class 2 residual solvents. For each test matrix, verification is needed to demonstrate reliability of the procedure, when the solvents that are present or potentially present in the sample are known, they can be determined using a limit test such as Procedure A or Procedure B, or by a quantitative test, such as Procedure C. When the solvents LTBP are not known, use the screening tests of Procedure A and Procedure B as required. Procedure A and Procedure B can separate most of the solvents. When the information about solvents LTBP in the material is known, the system suitability requirements only need to be demonstrated for the solvents expected to be present. Several residual solvents listed in this are not detected at the limit concentration using the analytical procedure described below. Those solvents include formamide, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, N-methylpyrrolidone, sulfolane, N,N-dimethylacetamide, and N,N-dimethylformamide. Those solvents should be determined using an alternative method that has been appropriately validated to demonstrate that the method is suitable for its intended purpose.

Class 3 Residual Solvents

Procedures A and B can separate most solvents in Classes 1, 2, and 3. However, the procedures have not been validated for Class 3 solvents, and appropriate validation will be required.

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 (Trifluoropropylmethyl Polysiloxane). 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-Dichloroethene, Carbon tetrachloride, 1,1,1-Trichloroethane, Methanol, 1,2-Dimethoxyethane, 1,1-Dichloromethane, Benzene, cis1,2-Dichloroethene, Trichloroethene, Acetonitrile, Chloroform, Toluene, 1,4-Dioxane, 1,2-Dichloroethane, 2-Hexanone, p-Xylene, m-Xylene, Nitro-methane, 2-Methoxyethanol, Pyridine, o-Xylene, Chlorobenzene, 2-Ethoxyethanol, 1,1,2-Trichloroethane, N, N-Dimethylacetamide, 1,2,3,4-Tetrahydroanaphthaleine, Ethylene glycol, 1-Methyl-2-pyrrolidinone, Dimethylformamide, Formamide 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.

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 precise.

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-Dichloroethene, 1,1-Dichloroethene, 1,1,1-Trichloroethene, Acetonitrile, Chlorobenzene, 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, Tetrahydrofuruan, 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, Methylthethyl ketone, Methylisobuty 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. 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.\(^6\)\(^7\)

**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 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 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-Dichloroethane, Methyleneethyl 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, precise, 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 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, because of its volatility of organic solvents and the excellent separating capability of capillary columns, it has governed the other analytical methods for RS determinations. It is no wonderment, that the pharmacopoeias have also adopted this excellent technique for RS determination. Gas Chromatography is very oftenly used in the detection of Residual Solvents. The choosing of injection system is determined by the sample type, the types of analytes, their quantity levels and available lab equipment.

**Loss of weight**

This method could be carried out at normal pressure and/or under vacuum. The loss of weight is a simple and not demanding method, but apart from that it has many disadvantages, including lack of specificity, high limit of detection (about 0.1%), and additionally a relatively huge quantity of sample needed to perform the tests. Moreover, atmospheric humidness will considerably modify the results obtained by the loss of weight technique. Nowadays, for this kind of determination, more sophisticated techniques like thermogravimetric analysis (TGA), differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are used.

**Infrared spectroscopy (IR) and Fourier Transform Infrared Spectrometry (FTIR)**

These techniques 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 that the high detection limit (above hundred ppm) and an absence of accuracy at low concentrations.

**Thermogravimetric Analysis (TGA)** is employed to estimate the concentration below 100ppm using only a few milligrams of substance.

**Differential Thermal Analysis (DTA) or Differential Scanning Colorimetry (DSC)**, are more sophisticated techniques that 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 and quantify residual solvent up to a very low detection limits.\(^13\)

**GC methods**

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, because of its volatility of organic solvents and the excellent separating capability of capillary columns, it has governed the other analytical methods for RS determinations. It is no wonderment, that the pharmacopoeias have also adopted this excellent technique for RS determination. Gas Chromatography is very oftenly used in the detection of Residual Solvents. The choosing of injection system is determined by the sample type, the types of analytes, their quantity levels and available lab equipment.

**Methods Accepted by Pharmacopoeias and ICH Guidelines**

The first analytical method for RS, which was published in pharmacopoeias, was a loss of weight.
**Method I**
- **Sample preparation**: Dissolved in water or other appropriate solvent to obtain concentration of about 20mg/mL of tested material. Additionally in method IV 5mL of sample solution is transferred to headspace vial.

**Method IV**
- **Column type**: 30m × 0.53mm column coated with a 5μm layer of a cross-linked phase G27 with a 5μm × 0.53mm guard column deactivated with phenylmethyl siloxane.
- **Carrier type**: Helium.
- **Injection port temperature**: 70°C.
- **Detector type**: Flame ionization detector.
- **Temperature program**: 35°C for 5min, then raised to 175°C with rate 8°C/min followed by raise to 260°C with rate 35°C/min and then maintained at 260°C for at least 16min.

**Method V**
- **Column type**: 30m × 0.32mm column coated with a 3.0μm layer of phase G43 with a 5μm × 0.53mm guard column deactivated with phenylmethyl siloxane.
- **Carrier type**: Appropriate to chosen column.
- **Injection port temperature**: 70°C, additionally headspace vial sealed at 80°C for 60min or as specified in individual monograph.
- **Temperature program**: 40°C for 20min Then increased rapidly to 240° And then maintained for 20min.

**Method VI**
- **Column type**: One of nine columns listed under <467> and specified in monograph.
- **Carrier type**: Appropriate to chosen column.
- **Injection port temperature**: 140°C.
- **Temperature program**: 70°C for 60min or as specified in individual monograph.

**1) Direct Injection**: The direct injection technique can be utilized when the sample which is tested is soluble in organic solvents (dissolution media) that has low boiling and all other components of sample and also evaporate at relatively low temperature. This method was found to be more time-consuming method than headspace chromatography.

**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.

**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 systems, several other techniques dealing with mixtures of solutes with similar volatilities in hyphenated techniques.

**Solid-phase microextraction**

Apart from the direct injection and the HS sampling systems, several other techniques dealing with injection problems have been developed. In SPME, the analytes are extracted into the stationary phase, which is attached to a length of fused silica fiber. The fiber is mounted in a syringe-like holder called an SPME fiber assembly, which protects the fiber during storage and penetration of septa in the sample vial and in the GC injector. When the equilibrium between the stationary phase (fiber) and the liquid phase or its headspace phase is reached, then the analytes adsorbed on the fiber are thermally desorbed in the injector of the GC and transferred onto the column. The selectivity of the fiber can be modified by changing the phase type or thickness according to the characteristics of the analytes.

**Single drop microextraction**

Another injection technique that relies on an indirect way of introducing analytes into a gas chromatograph, is a single
drop microextraction (SDME), known also under the term liquid microextraction (LME). It is often used as a simple and inexpensive alternative to the SPME technique because it does not require any complicated equipment, only a typical microsyringe and a small amount of organic solvent. This relatively new technique combines classic liquid extraction and solid phase microextraction. It uses a small volume of solvent suspended as a drop at the end of the microsyringe needle in the headspace phase over the sample solution. A drop size is preferred to be in the range 1 ñ 3 µL, what means that the surface of a liquid drop is larger than the surface of an SPME fiber and the extraction process is relatively faster. The extraction surface of the drop is critical for the analysis. When the drop is bigger the extraction efficiency is higher, but also the stability of such a drop (loss of four drops out of ten) is lower and the reproducibility (CV 60%) decreases. There are many solvents with different polarities that can be used as extracting solvents. 16

**GC separation mode**

For separation step, capillary (narrow-bore) and wide-bore columns (known conjointly as open cannular columns) are used. Because of their separation prospects and little sample capability, they much outmoded packed columns. Capillary columns contain an extended tube that may be made from metal, glass or quartz, the diameter of which can be within the vary from fifty to five hundred µm, and also the length typically from five m to two hundred m. The capillary is coated within with a thick compound film of the stationary phase. The area unit varied stationary phases. Most of them area unit high mass, thermally stable polymers that area unit liquids or gums. The foremost common stationary phases of this sort area unit the polysiloxanes and synthetic resin glycols. Another common form of stationary phases, area unit tiny porous particles composed of polymers or zeolites (e.g., alumina, molecular. vital characteristic of the capillary columns is their tiny flow ohm resistance relative there to of the packed columns. This allows terribly long columns to be used and so, provides terribly high efficiencies or instead, terribly short columns operated at terribly high mobile part velocities, to supply in no time separations. The foremost recent area unit capillary columns that area unit terribly sturdy, terribly inert and might be used over a large vary of temperatures what makes them the foremost oftentimes used columns all told of GHz analyses. Nowadays, the selection of capillary columns is incredibly wide and suppliers provide several columns with totally different stationary phases dedicated to special analysis like residual solvents determinations. The optimum column choice for residual solvents determination, isn’t terribly difficult typically once the suppliers provide their columns a long side prescribed strategies for separation of analytes of interest. The foremost in style stationary phases used for RS determinations area unit given. 17

**GC detection mode**

The next step in each GHz analysis may be a detection method. The unit area several devices used for this task. In general, GHz detectors area unit four to five orders of magnitude a lot of sensitive than LC detectors and so, area unit ideal for trace analysis. The area unit several detection strategies that may be used, as well as the activity of the quality physical properties, like thermal physical phenomenon and lightweight absorption to a lot of specific properties, like ionization potential and also the heat of combustion. The necessities for a GHz detector depend upon the applying for residual solvents analysis, within the scenario once analytes gift within the sample area unit far-famed, or suspected, the flame-ionization detector (FID) is usually recommended. The FID detector uses atomic number 1 and air because the combustion gases, that area unit mixed with the column eluent (helium, element or alternative acceptable gas) and burned in a very tiny jet set within a cylindrical conductor. to boot, a possible of a couple of hundred volts is applied between the jet and also the conductor which ends in grouping the electron/ion pairs obtained once the burning of carbon containing product. The FID detects all carbon containing molecules, with the exception of tiny molecular compounds like compound, monoxide and it may be thought-about as a universal detector. Generally, it’s become the foremost oftentimes used detector in GHz due to its low detection limits (210-12 g/s), wide linear dynamic varies (< 107), and general responsiveness and utility, particularly for trace organic compounds like residual solvents.

In things once analytes area unit unknown and extra level of identification capability is required, spectrometer (MS) detectors area unit preferred. In general, the MS detectors capture, ionize, accelerate, deflect, and find the ionized molecules. It happens by breaking every molecule into ionized fragments and police investigation these fragments exploitation their mass charge magnitude relation. Detection limits obtained with this sort of detector in single particle observance mode (SIM) are able to do 10-12 ñ 10-15 g limits with linear vary regarding one hundred and five. It may be either universal in its scan mode or selective in particle observance mode (SIM). Another detector that finds application in GHz, is that the negatron capture detector (ECD). It’s a selectable and really sensitive detector (2 ñ 10-13 g utilized only if compounds with halogens or alternative negatron capturing team area unit analyzed. The area unit alternating universal or detectors in use, like: photoionization detector (PID), thermal physical phenomenon detector (TCD), thermoionic emission detector (TID), flame measuring detector (PID), hall electrolytic physical phenomenon detector, thermal energy instrument (TEA), Fourier rework infrared detector (FT-IR), element phosphorus detector (NPD).18–20

**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


