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ORGANIC VOLATILE IMPURITIES IN PHARMACEUTICALS

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ABSTRACT

In pharmaceuticals, Organic volatile impurities (OVIs) are residual solvents that are used in and are produced during synthesis of drug substances, or in excipients used in the production of drug formulations. These residual solvents are potentially undesirable substances, they either modify the properties of certain compounds or are hazardous to the health of individual. OVIs(Organic volatile impurities) also affect physico-chemical properties of the bulk drug substance. The intention of this paper was to review and discuss some of the current analytical procedures including gas chromatographic (GC) and other alternative techniques which are used for residual solvents determination. GC methods have been developed to monitor this kind of impurities routinely. The most popular techniques of sample introduction into the gas chromatograph include direct injection, static or dynamic headspace, solid-phase micro extraction and single drop micro extraction.

INTRODUCTION

Organic volatile impurities are **r**esidual solvents that are used in and are produced during synthesis of drug substances, or in excipients used in the production of drug formulations. Many of these residual solvents generally can not be completely removed by standard manufacturing process or techniques and are left behind, preferably low levels [1].

The determination of residual solvents in drug substances, excipients or drug products is known to be one of the most difficult and demanding analytical tasks in the pharmaceutical industry. Further more, the determination of polar residual solvents in pharmaceutical preparations continues to present analytical challenge mainly because these compounds are quite difficult to remove from water or polar solvents. Organic volatile impurities may arise during the manufacture or storage of new substance. They may be identified or unidentified, volatile or non-volatile; include starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. Apart from the use of solvents in the manufacture of drug substances, large quantities of organic solvents are frequently used to dissolve film coating materials such as methyl cellulose and ethyl cellulose to facilitate application on to compressed tablets. Hence the evaluation of Organic volatile impurities (OVI's)is considered as an important tool in the quality control of pharmaceuticals [2].

Presently in the pharmaceutical industries, special importance is given for residual solvents testing. As these residual solvents are potentially undesirable substances ,they either modify the properties of certain compounds or are hazardous to the health of the individual. OVIs also affect physico-chemical properties of the bulk drug substance [3].

Crystallinity of the bulk drug can be affected, as difference in the crystal structure of the bulk drug may

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lead to change in dissolution properties and problems with formulation of the finished product. Finally, residual solvents can create odour problem and colour changes in the finished products [4].

SCOPE

Residual solvents in drug substances, excipients and drug products fall in the scope of ICH guidelines, if production or purification process involves the use of such solvents. The product should then be tested for the residual solvents. A cumulative method may be used to calculate the residual solvent level in drug product on the basis of their levels in the ingredients that are used to produce the final drug product. If the cumulative levels are below or equal to the recommended levels in the guidelines, the drug product need not be tested for residual solvents [5].

However, If the cumulative levels are above the recommended level, the drug product must be tested for residual solvents to ensure that the manufacturing and purification processes, have reduced the levels to be within the acceptable range. The ICH guideline does not apply to potential new drug substances, excipients or drug products used during the clinical research stages of development. It also does not apply to existing drug products in the market. The guidelines do, however, apply to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as therapies of short duration (less than 30 days) or topical application, with proper justification made on case-by-case basis [6].

SOURCES OF RESIDUAL SOLVENTS IN A DRUG PRODUCT

In a task of effectively removing or decreasing the amount of organic solvents present in a drug product it is necessary to investigate ways the drug is contaminated by the solvents. Before a pharmaceutical company obtains the final product tablets, capsules or other pharmaceutical form, some elemental stages have to be performed:

a. synthesis of an Active Pharmaceutical Ingredient(API),
b. Production of a drug product (DP),
c. Packaging [7].

At each of these stages the product can be potentially contaminated with organic solvents. Stages marked with thicker frames are processes where organic solvents may be in use or where a pharmaceutical substance or product may become contaminated with organic solvents(packaging). Sometime the source and means of contamination determine the way of removing them or reducing their quantity.

For example, if the solvent is occluded in crystals of an API, recrystallization should be performed and if the solvent is adsorbed on a surface of particles, a drying procedure is recommended [8].

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health based exposure limit is needed. Class 3 solvents have PDE's of 50 milligrams (mg) or more per day [9].

LIMITS OF RESIDUAL SOLVENTS

Solvents to be avoided

Solvents in class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.

However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. The solvent 1, 1,1-tetrachloro ethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data [10-12].

Solvents to Be Limited

Solvents in Table 2 should be limited in pharmaceutical substance or products because of their inherent toxicity. PDEs are given to the near 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Solvents with low toxic potential

Solvents in class 3 may be regarded a less toxic and of lower risk to human health. Class 3 includes no solvent known as human health hazard at levels normally accepted in pharmaceuticals [13-15].

However, there are no long term toxicity or carcinogenicity studies for many of the solvents in class 3. Available data indicate that there 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 per day or less (corresponding to 5000 ppm or 0.5% under option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

Solvents for which No adequate Toxicological Data was Found

The following solvents (Table 4) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDF was found. Manufactures should supply justification for residual levels of these solvents in pharmaceutical products.

Toxicity of residual solvents in pharmaceuticals

Exposure limits in guideline are established by referring to methodologies and toxicity data described in Environmental Health Criteria (EHC) and the Integrated Risk Information System (IRIS) monographs. However, some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. Patients (not in general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infections or diseases, The assumptions of life time patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.

Residual solvents should not exceed recommended levels, except in exceptional circumstances. Data from toxicological studies that are used to determine acceptable levels for residual solvents should be generated using appropriate protocols ,such as those described for example, by recognization for Economics co-operation and Development (OECD) and the US Food and Drug Administration (FDA) Red Book [16].

As per ICH Guidelines the solvents used in the manufacturing of drug substances have been classified into 4 types ,viz, class 1, class 2, class 3 and class 4. Solvents in class 1 should not be employed in the manufacture of drug substances and excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effects. Solvents and their permissible concentration limits (in ppm) are benzene (2), carbon tetra chloride (4), 1,1-dichloroethane (1500).While 1,2-dichloroethane, 1,1-dichloroethane and carbon tetrachloride are toxic, benzene is carcinogenic; and carbon tetrachloride and 1,1,1-trichloroethane are potential environmental hazards. However if their use is unavoidable in order to produce a medicinal product with a significant therapeutic advancement, then their levels should be restricted as described above.

Solvents in class 2 should be limited in pharmaceutical products because of their inherent toxicity. List of class 2 solvents with permissible daily exposure limits and concentration limit (ppm) are reproduced.

Solvents in class 3 are less toxic and of lower risk to human health. Class 3 does not include any solvents that are considered as health hazard to humans at levels normally accepted in pharmaceuticals. However there are no long term toxicity or carcinogenicity studies for many of the Solvents in class 3.Available data indicate that they are less toxic in acute or short term studies and have no results in genotoxicity studies. Class 3 solvents are Acetic acid, Heptanes, Acetone, Isobutyl acetate, Anisole, Isopropyl acetate, 1-butanol , Methyl acetate, 2-Butanol, 3-Methyl-1-butanol, Butyl acetate, Methyl ethyl ketone, Tert–Butylmethyl ether, Methylisobutylketone, Cumene, 2-Methyl-1-propanol, Dimethylsulfoxide, Pentane, Ethanol, 1-Pentanol, Ethylacetate, 1-Propanol, Ethyl ether, 1-Propanol, Ethyl formate, Propyl acetate, Formic acid, Tetra hydro furan.

No adequate toxicological data is available for solvents classified as class 4 solvents. These solvents are 1,1-Diethoxy propane, Methyl isopropyl ketone, Petroleum ether, Iso octane, Tri chloro acetic acid, Isopropyl ether, Tri fluoro acetic acid, 1,1-Dimethoxy propane, Methyl tetra hydro furan, 2,2-Dimethoxy propane. The manufacturers should justify the residual levels of these solvents in pharmaceutical products. Such solvents are prohibited from being used during the manufacture of excipients or medicinal products.

METHODS FOR ORGANIC VOLATILE IMPURITY (OVI) ANALYSIS

The OVI analyses include loss on drying (LOD) thermogravemetric analysis (TGA), spectroscopic and spectrometric methods and gas chromatographic methods.

Loss on Drying (LOD)

In this method, the amount of volatile components released from a sample under specific temperature or vacuum condition is determined by loss on drying .LOD suffers from the main disadvantage of being nonspecific. Other disadvantages are that atmospheric humidity can cast doubt on the experimental results and that a large quantity of material must be used for the test. Usually 1g or more of the material is used for a typical test to achieve a detection limit of 0.1%(w/w) or less.

Thermo gravimetric analysis (TGA)

The loss of volatile components from a sample when subjected to a temperature gradient is measured .The disadvantage of these methods is that they do not speciate and account for volatile approximately 100 ppm can be obtained, using only few mg of the sample.

Spectroscopic and spectrometric methods

These have generally lacked the low detection limits needed for toxic residual solvents, although the detection limits would be applicable for ICH class 2 and class 3 solvents. In case of infrared spectroscopy (IR), detection above 100 ppm and lack of accuracy at low concentration of residual solvents have been reported.

Osawa and Aiba used infrared spectroscopy to determine the levels the tetrahydrofuran (THF), dichlorobenzene and methylene chloride in polymer samples by measuring the characteristic solvent bands in spectra.

Gas chromatographic methods

Gas chromatography. Gas chromatographic procedures for OVIs can be carried out either by direct injection method, head space analysis, solid phase micro extraction method and the new technique known as single drop micro extraction (SDME).

Direct Injection Method

This technique involves injecting the entire liquid sample, via a syringe, into a heated port where the sample is rapidly vaporized and then carried on to the capillary .The simplicity and low cost of direct Injection has led to the resurgence of this technique. The advantages of direct Injection method are less adsorption of active compounds, less discrimination against high boiling compounds and better sensitivity for trace compounds.

These injection techniques can also be used for concentrated samples commonly analysed on splitter systems, if the sample is first diluted with a solvent and injection is kept low to prevent column overload. The solvents used are water dimethyl formamide (DMF), DMSO and benzyl alcohol. Water has advantage of having no solvent peak when the flame ionization detector (FID) is used.DMF, DMSO and benzyl alcohol have higher boiling points than those of the volatile analyte this allows the elution of the solvent peak after the analyte residual solvent peaks [4-6].

Head space Gas chromatography

Head space sampling technique can be categorized into two types dynamic head space and static head space analysis. In dynamic head space technique, a continuous flow of gas is swept over the surface of a sample matrix. Volatile from sample matrices are conveyed into a trap where the volatile residual solvents are accumulated prior to analysis.

A thermal desorption cycle of the trap is initiated, and a carrier gas takes the analyte into a gas chromatography for the analysis .In static head space technique, equilibrium between the volatile components of liquid or solid sample and the surrounding gas phase in a sealed vessel Is established. Aliquots of gas phase are injected into gas chromatograph for analysis.

According to the principle of head space gas chromatography, the sample containing volatile components is placed in a sealed vial and conditioned until the volatile components portion into the vapours phase above the sample and reach equilibrium.

G= gas phase (Head space)

The gas phase is commonly referred as the head space and lies above the condensed sample phase

S = sample phase

The sample phase contains the compound(s) of interest. It is usually in the form of a liquid or solid combination with a dilution solvent or matrix modifier [12].

Once the sample phase is introduced into the vial and the vial is sealed, volatile components diffuse into the gas phase until the head space has reached a state of equilibrium as depicted by the arrows. The sample is then taken from head space.

As a result of their concentration in the vapour phase is a function of the concentration in the original mixture. capillary gas chromatography, with static head space sampling (HS-GC)is widely used in the field of forensic, clinical, food and aroma analysis.

This technique is robust, convenient and readily automated and validated is the most common method for the control of residual solvents in pharmaceuticals. It has been adopted, as a recommended method for the pharmaceuticals in the European pharmacopoeia (ph Eur) and the United States Pharmacopoeia (USP). HS-GC has become the preferred technique for the analysis of residual solvents in bulk pharmaceuticals and finished products.

Advantages of (HS-GC) sampling are substantially more robust, since less of the dissolution medium is introduced onto the column. Dynamic and static HS analysis has the advantage of avoiding equilibrium between the gas and sample. The head space technique are very convenient way of cleaning up a sample before the actual GC analysis .It is preferred if standard GC procedures cause problems with the sample matrix in respect of solubility or thermal stability.

Use of HS-GC even permits the successful analysis of liquid samples, if the partition coefficient of the volatiles is low enough to shift the equilibrium to the gas phase. It is acceptable for samples not able to be handled in a syringe, such as solid or extremely dirty material.

HS analytical has the advantages of ease of use and automation. Disadvantage of head space chromatography, head space analysis has low detection limits are higher boiling volatiles and semi volatiles are not detectable with this technique, due to their low partition in the gas head space volume.

HS analytical technique is only useful, if the residual solvents are simply adsorbed onto the surface of the drug, as it cannot dissolve the solvent occluded within in the crystals. The sensitivity of the head space technique is limited to ppm levels. Multiple head space extraction of the sample provides total organic volatile impurity content of the sample, and is immune to matrix effect [10].

Solid phase micro extraction (SPME)

It involves extraction of specific organic analyte directly from head space of the samples in closed vials, onto a fused silica fiber coated with polydimethyl siloxane the polymeric liquid phase , polydimethyl siloxane or polyacrylate. After equilibration, the fiber containing the adsorbed or absorbed analyte(s) is removed and thermally desorbed in the hot injector of a GC using appropriate

column and detector with or without cryofocusing.

The technique is very simple, fast and does not employ any organic solvents either for sample preparation or cleanup. The SPME method has been developed for the analysis of polar residual solvents in pharmaceutical preparations.

The most important step for successful residual solvent analysis is the development of a stable, selective, sensitive and precise method of analysis of compounds with different volatility and polarities. SPME was introduced by pawliszyn as a solvent free alternative for extraction of organic compounds from water samples.

More recently, SPME has gained popularity for determination of organic impurities in pharmaceutical compounds. SPME is a solvent less technique for the extraction of analyte from different matrices.

Single drop micro extraction (SDME)

The use of a new sampling method for gas chromatography, SDME is applied to both manual and automated modes. The technique of SDME has found wide acceptance because it is simple and inexpensive .More recently, SDME has been evaluated as an alternative to SPME.

In this technique, a micro drop of solvent is suspended from the tip of a conventional micro syringe and is immersed in a sample solution in which it is immiscible or suspended in the head space above the sample.

The original application used an 8 µl drop of n-octane in an aqueous sample, and only a fraction of this drop was analyzed subsequently by gas chromatography. Later, a small drop was used (1 or 2 µl) and all of it was injected .It is also called as head space solvent micro extraction or head space liquid phase micro extraction [7]. Head space SDME is similar to traditional head space sampling in that volatiles are sampled from the vapors above the sample, thus avoiding interferences from the sample matrix. A variety of methods and specialized equipment is available for this purpose.

In head space SDME, the fiber used in SPME is replaced by liquid micro drop that can also be chosen for its selectivity. The ranges of reported analyses include alcohols, chlorobenzenes, trihalomethanes, and BTEX (benzene, toluene, ethyl benzene and xylenes).

The extraction of solvents that have been used for liquid-liquid SDME are hexane ,n-octane, iso- octane, cyclo hexane, n- hexadecane, toluene, chloroform, butyl acetate, di-isopropyl ether. For head space SDME, the solvents are n-octane, n-decane, tetradecane, n-hexadecane, tolune,o- xylene, cyclohexane, 1- octanol, benzyl alcohol, ethylene glycol, di-ethyl phthalate.

Parameters that have been considered for SDME are size of the drop, shape of the needle tip, temperature of sampling, equilibration time, sampling time, effect of stirring, and ratio of head space volume to sample volume. Advantage of head space SDME are high selectivity provided by wide range of extracting solvents, good quantization and low detection limits. Fresh solvent for each sample eliminates sample carry over. Liquid extract an operates by absorption, resulting in high upper limit of detection and minimal competition among analytes. It is simple, fast and easy and involves minimal sample preparation.

Initially, USP methods for the analysis of organic volatile impurities in pharmaceuticals was carried out by three methods, I, II and III. Later three additional methods were included which are the methods IV, V and VI. In method I, the sample is analyzed by direct aqueous injection technique with FID detector using G-27 column (5% phenyl and 95% methypolysiloxane, 30 mx0.53 mm). In method II, the sample is analyzed by dynamic head space technique with FID detector using G-25 column (1% polyethylene glycol)packed column. In method III, the sample is analysed by dynamic head space technique with mass selective detector using G-25 column (1% polyethylene glycol) packed column. In method IV, the sample is analysed by static head space technique with FID detector using G-43 column (6% cyanopropylphenyl and 94% dimethyl polysiloxane) 30 mx0.53 mm. In method V, the sample is analysed by direct aqueous head space technique with FID detector using G-43 column (6% cyanopropylphenyl and 94% dimethyl polysiloxane) 30 mx0.53 mm. In European pharmacopoeia, three diluents, viz, water, N,N-dimethyl formamide (DMF) and 1,3-dimethyl-2-imidazolidinone (DMI) are used for sample preparation. Two chromatographic system s are prescribed, but system A Is preferred while system B is used normally for confirmation or identity [11].

System A uses a fused capillary or wide bore column of 30x0.32 or 0.53 mm i.d., (6% poly cyanopropylphenyl siloxane and 94% dimethyl polysiloxane) with FID or ECD detector ,using static head space technique with temperature programming.

System B uses a fused capillary or wide bore column of 30x0.32 or 0.53 mm i.d., coated with macrogel 20000R film of thickness 0.25 mm with FID or ECD detector, using static head space technique with temperature programming. The choice of sample preparation procedure depends on the solubility of the substance to be examined and in certain cases residual solvents to be controlled. Various methods have been reported for the simultaneous estimation of residual solvents .An analytical method for extracting and determining 32 ICH class 2 and class 3 residual solvents using static head space sampling, a new technology known as Stop-Flow GC has been reported. A Stop-Flow GC, in combination with the proper choice of column stationary phases, has been used to improve other difficult separations.

High–speed separation of 36 residual solvents has been demonstrated in a single chromatographic run, using

a combination of polyethylene glycol stationary phase and trifluropropyl stationary phase.

The separation was accomplished in 12 min. Resolution between co eluting or closely eluting components was substantially improved by introducing nine Stop-Flow pulses to tune the chromatographic separation.

Teledyne Tekamah 7000HT head space auto sampler unit in conjugation with Stop-Flow GC technology has been used for separation of class1 and class 2 residual solvents. In Stop-Flow GC, the solvents were separated by passing the sample through a two-column ensemble consisting of Stabilwax column and an Rtx-200 cokumn coupled in series.

Carrier gas flow through the second (Rtx-200) column was interrupted briefly (Stop-Flow pulses) to tune the separation at the outlet of the column ensemble [12].

Environmental regulation of organic volatile impurities

Several of the residual solvents frequently used in production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and the Integrated Risk Information System (IRIS).The objectives of such groups as the IPCS ,the U.S. Environmental protection Agency(EPA),and FDA include the determination of acceptable exposure levels .The goal is protection of human health and maintenance of Environmental integrity against the possible deleterious effects of chemicals resulting from long term Environmental exposure. The methods involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach such as use of larger safety factors .The approach described therein relates primarily to long term or lifetime exposure of the general population in the ambient environment, i.e., ambient air, food, drinking water and other media.

Residual solvents in pharmaceuticals

Exposure limits in this guideline are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. Some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. They are as follows

- Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
- The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
- Residual solvents are unavoidable components in pharmaceutical production and will often be a part of drug products.
- Residual solvents should not exceed recommended levels except in exceptional circumstances.
- Data from toxicological studies that are used to determine acceptable levels for Residual solvents should have been generated using appropriate protocols such as those described, eg, by the Organization for Cooperation and Development, EPA, and the FDA red book [17].

Table 1. Class 1 solvent in pharmaceutical substance or product (solvents that should be avoided)

S. No	Solvents	Concentration limit(ppm)	Concern
1	Benzene	2	Carcinogen
2	Carbon tetra chloride	4	Toxic & environmental hazard
3	1,2-dichloro ethane	5	Toxic
4	1,1-dichloro ethane	8	Toxic
5	1,1,1-tri chloro ethane	1500	Toxic

Table 2. Class 2 solvents in pharmaceutical products

S. No	Solvents	PDE(mg/day)	Concentration limit(ppm)
1	Acetonitrile	4.1	410
2	Chlorobenzene	3.6	360
3	Chloroform	0.6	60
4	Cyclohexane	38.8	3880
5	1,2-dichloroethane	18.7	1870
6	Dichloromethane	6.0	600
7	1,2-dimethoxyethane	1.0	100
8	N,N-Dimethyl acetamide	10.9	1090
9	N,N-Dimethyl formamide	8.8	880
10	1,4-Dioxane	3.8	380
11	2-Ethoxy ethanol	1.6	160

12	Ethylene glycol	6.2	620
13	Formamide	2.2	220
14	Hexane	2.9	290
15	Methanol	30.0	3000
16	2-methoxy ethanol	0.5	50
17	Methoxy butyl ketone	0.5	50
18	Methyl cyclo hexane	11.8	1180
19	N-Methyl pyrrolidine	48.4	4840
20	Nitro methane	0.5	50
21	Pyridine	2.0	200
22	Sulfolane	1.6	160
23	Tetra line	1.0	100
24	Toluene	8.9	890
25	1,1,2-tri chloro ethane	0.8	80
26	Xylene	21.7	2170

Table 3. Class 3 solvents which should be limited by GMP or other quality based requirements

S.NO	Solvents	S.NO	Solvents
1	Acetic acid	15	Cumene
2	Heptanes	16	2-Methyl-1-propanol
3	Acetone	17	Dimethylsulfoxide
4	Isobutyl acetate	18	Pentane
5	Anisole	19	Ethanol
6	Isopropyl acetate	20	1-Pentanol
7	1-butanol	21	Ethylacetate
8	Methyl acetate	22	1-Propanol
9	2-Butanol	23	Ethyl ether
10	3-Methyl-1-butanol	24	1-Propanol
11	Butyl acetate	25	Ethyl formate
12	Methyl ethyl ketone	26	Propyl acetate
13	Tert –Butyl methyl ether	27	Formic acid
14	Methylisobutylketone	28	Tetra hydro furan

Table 4. Solvents for which No adequate Toxicological Data was found

S.NO	Solvents	S.NO	Solvents
1	1,1-Diethoxy propane	6	Petroleum ether
2	Methyl isopropyl ketone	7	Iso octane
3	1,1-Dimethoxy propane	8	Tri chloro acetic acid
4	Methyl tetra hydro furan	9	Isopropyl ether
5	2,2-Dimethoxy propane	10	Tri fluoro acetic acid

Fig1. Schematic diagram of auto injector

Fig 2. Schematic diagram of sealed vial

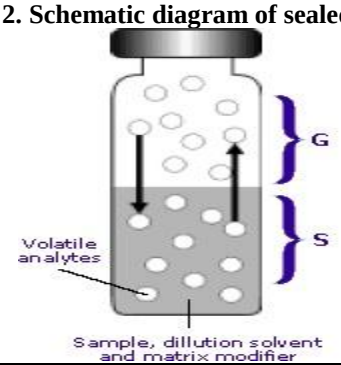

Fig 3. Schematic diagram of HS-GC

CONCLUSION

The residual solvents (RS) analyses include loss on drying (LOD), thermogravemetric analysis (TGA), spectroscopic and spectrometric methods and gas chromatographic methods. The most useful analytical method of choice for identification and quantification of RS, is the gas chromatography (GC). Gas chromatographic procedures for RS can be carried out either by direct injection method, head space (HS) analysis, solid phase micro extraction (SPME) method or the new technique known as single drop micro extraction (SDME). Although the direct injection is the simplest and the cheapest option, it should be excluded when samples with complex matrices are analyzed. For the separation process undoubtedly capillary columns dominated GC. When in-process analysis requires short time, narrower and shorter or multicapillary columns can be used.

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