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REGULATORY AND ANALYTICAL ASPECTS OF RESIDUAL SOLVENTS IN AYURVEDIC FORMULATIONS-A RECENT UPDATE

Jyoti Solanki[1], Meenu Mehta[1], Saurabh Satija[1], Munish Garg[1*]

*Dr. MunishGarg, Associate Professor, Room No. 229, Department of Pharmaceutical Sciences, MaharshiDayanand University, Rohtak-124001, Haryana, India.

Email: mgarg2006@gmail.com

ABSTRACT

Residual solvents are potentially undesirable substances in herbal formulations when present above the permissible limits given by ICH guidelines in 1997 and they must be regulated properly in order to avoid their deleterious health effects. The present paper provides a recent update on the regulations for residual solvents, different Pharmacopoeial guidelines and analytical techniques available for the screening of residual solvents.

KEYWORDS Analytical techniques, herbal formulations, residual solvents.

INTRODUCTION

Herbal drugs and formulations as a potential source of therapeutic aids have attained a significant role in health system all over the world[1]. Herbal drug formulations which are comminuted or powdered, extracts, tinctures, fatty or essential oils, expressed juices, processed resins or gums, etc. prepared from raw herbal plants, are currently in demand and their popularity is increasing day by day. but at the same time several types of impurities are being incorporated intentionally or unintentionally in herbal formulations for different reasons[4].As per ICH guidelines for "impurities in new drug substances" impurities are classified into three categories as organic impurities, inorganic impurities and residual solvents. Organic and inorganic impurities can arise during the manufacturing process and/or storage of the new drug substance. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products.These residual solvents are potentially undesirable substances when present above the permissible limits and may lead to hazardous effects to the health of the individual[5].Residual solvents pose a great risk to human health when present above the permissible limits specified by ICH guidelines on residual solvents. So it is must for the regulatory agencies to look for the proper regulation of these guidelines. The present study was carried out to review the status of the regulatory agencies for residual solvents, acceptance of the ICH guidelines by different pharmacopoeias, tolerable daily intake of these residual solvents and also to specify the analytical methods to be used for the screening of residual solvents in pharmaceuticals.

LIMITS OF RESIDUAL SOLVENTS

As per ICH guidelines, residual solvents have been classified into the four types (Table 1) based on their toxicity criteria and also have given acceptable limits for them (Table 2). Class 4 solvents including Methylisopropyl ketone, Methyltetrahydrofuran, Petroleum ether, Trichloroacetic acid, Trifluoroacetic acid, Isopropyl ether, 1,1-Diethoxypropane, 1,1-Dimethoxymethane, 2,2-Dimethoxypropane and Isooctane were not found to have any toxicity data, so no limits were imposed on them.

Residual solvent class	**Indication**	**Claim**	**Remark**
Class 1	Solvents to be avoided	Known human carcinogens Strongly suspected human carcinogens Environmental hazards	If unavoidable, then their levels should be restricted as per the limits given by ICH guidelines.
Class 2	Solvents to be limited	Non-genotoxic animal carcinogens or Possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity	Permitted daily exposures (PDEs) are given to the nearest 0.1 mg/day.
Class 3	Solvents with low toxic potential	No health based exposure limit is needed	Less toxic in acute or short term studies; 50 mg/day (5000 ppm) or less was found acceptable.
Class 4	solvents with no toxicological data	No health based exposure limit is needed	Do not have any toxicological data and hence no prescribed limits are there.

Table 1: Classification of residual solvents

Class 1		**Class 2**		**Class 3**	
Solvent	**Limit (ppm)**	**Solvent**	**Limit (ppm)**	**Solvent**	**Limit (%w/w)**
Benzene	2	Acetonitrile	410	Acetic acid	0.5
Carbon tetrachloride	4	Chlorobenzene	360	Acetone	0.5
1,2-Dichloroethane	5	Chloroform	60	Anisole	0.5
1,1-Dichloroethene	8	Cyclohexane	3880	1-Butanol	0.5
1,1,1-Trichloroethane	1500	1,2-Dichloroethene	1870	2-Butanol	0.5
------	----	Dichloromethane	600	Butyl acetate	0.5
------	----	1,2-Dimethoxyethane	100	*t*-Butylmethyl ether	0.5
------	----	N,N-Dimethylacetamide	1090	Cumene	0.5
------	----	N,N-Dimethylformamide	880	Dimethylsulfoxide	0.5
------	----	1,4-Dioxane	380	Ethyl acetate	0.5
------	----	2-Ethoxyethanol	160	Ethyl ether	0.5
------	----	Ethylene glycol	620	Ethyl formate	0.5
------	----	Formamide	220	Formic acid	0.5
------	----	Hexane	290	Heptane	0.5
------	----	Methanol	3000	Isobutyl acetate	0.5

*ICH Q3C, 1997	------	----	2-Methoxyethanol	50	Isopropyl acetate	0.5
	------	----	Methylbutyl ketone	50	Methyl acetate	0.5
	------	----	Methylcyclohexane	1180	3-Methyl-1-butanol	0.5
	------	----	N-Methylpyrrolidone	4840	Methyl ethyl ketone	0.5
	------	----	Nitromethane	50	Methylisobutyl ketone	0.5
	------	----	Pyridine	200	2-Methyl-1-propanol	0.5
	------	----	Sulfolane	160	Pentane	0.5
	------	----	Tetralin	100	1-Pentanol	0.5
	------	----	Toluene	890	1-Propanol	0.5
	------	----	1,1,2-Trichloroethene	80	2-Propanol	0.5
	------	----	Xylene	2170	Propyl acetate	0.5
	------	----	------	----	Tetrahydrofuran	0.5

Table 2: Limits of residual solvents as provided by ICH*

REGULATIONS FOR RESIDUAL SOLVENTS

The impurities in Pharmaceuticals are regulated by Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) guidelines. Because many solvents pose a major risk to human health, national and international regulatory bodies such as the United States Food and Drug Administration (U.S. FDA), the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), and the International Conference on Harmonization (ICH) require analysis for residual solvents in pharmaceutical drug substances, excipients and final products. In herbals,residual solvents may results from their use as an extraction solvent in liquid extracts and tinctures or when added as a diluents to liquid pharmaceutical preparation.

A number of organic solvents such as methanol.ethanol, acetone, benzene, cyclohexane etc. are used for manufacturing herbal medicines, and can be detected as residues of such processing. These are known as residual solvents or organic volatile impurities. They should be controlled through good manufacturing practices (GMPs) and quality control. For the proper regulation, World health organization (WHO) has provided guidelines for accessing the quality of herbal medicines

with respect to these residual solvents. The term "permitted daily exposure" (PDE) is proposed by WHO defining the maximum acceptable intake per day of residual solvent in pharmaceutical products.

Food and Drug Administration in 1997 published the ICH guidance for industry, Q3C "Impurities: Residual Solvents" (ICH Q3C)for the future control and regulation of residual solvents in herbals and other pharmaceuticals. These guidelines recommend the use of less toxic solvents, set criteria for analytical methods used to identify and quantify residual solvents as well as provide acceptable concentration limits for them. Exposure limits in guideline (ICH Q3C, 1997) are established by referring to methodologies and toxicity data described in Environmental Health Criteria (EHC) and the Integrated Risk Information System (IRIS) monographs.

PHARMACOPOEIAL STATUS

Different pharmacopoeias have different aspects in regards to residual solvents but most of the pharmacopoeia has adopted the ICH guidelines for their proper regulation. The following summarizes the status of different pharmacopoeia:

United States Pharmacopoeia (USP)

In 1988, the United States Pharmacopoeia (USP) provided control limits and testing criteria for seven organic volatile impurities (OVIs) under official monograph no. 467 but before 1997, these guidelines were not fully implemented in the actual testing done in the pharmaceutical industry. In July 2007 USP has fully adopted ICH guidelines for residual solvents**.** USP in vol. 30 have published a major revision to monograph no. 467 effective from July 1, 2008 in which required concentration limit is determined from the maximum daily exposure (MDE) based upon a daily dosage of 10 g of the final drug product and solvents requiring testing were increased from seven to fifty-nine (USP).

European Pharmacopoeia (EP)

The European Pharmacopoeia (EP) has fully adopted ICH guidelines regarding residual solvents under title "Identification and control of residual solvents" in 1997. In EP two procedures (systems) A and B are presented. System A is preferred for identification while system B is employed normally for confirmation of identity. Gas chromatography with headspace injection is proposed in both systems. For water-soluble samples, water is proposed as a solvent, for water-insoluble substances N, N-dimethylforamide (DMF), N,Ndimethylacetamide, 1,3-dimethyl-2-imidazolidinone (DMI) is suggested as a solvent.

In case of class 1 residual solvents, they are usually not mentioned in specific monograph in EP unless it is known that certain sources are unavoidably prepared using a Class 1 solvent and this information is also confirmed by the competent (regulatory) authorities. Class 2 solvents are not mentioned in specific monographs because they are controlled by the general monograph in accordance with ICH limits. Class 3 solvents are mentioned in the monograph only where they occur at levels > 0.5% (ICH).

Japanese Pharmacopoeia (JP)

The JP volume XIV has adopted the ICH guidelines for residual solvent determination. JP defines residual solvents as those residual organic solvents in pharmaceuticals that should be tested using gas chromatography to comply with the limits specified in the ICH Harmonized Tripartite Guideline.

Indian Pharmacopoeia (IP)

Indian Pharmacopoeia is still lacking in control of residual solvents in herbals as well as other pharmaceuticals and does not give any information regarding their regulation, control or identification.

Analytical techniques for residual solvent determination

Different analytical techniques are available for the estimation of residual solvents in herbals including gravimetric analysis i.e. Loss on Drying (LOD), Thermo Gravimetric Analysis (TGA), Differential Thermal Analysis (DTA) or Differential Scanning Calorimetry (DSC), thermal desorption (TD)-GC/MS, ChemSensor and some spectrometric and spectroscopic procedures. But Gas chromatography based test procedures are the most popular and are chemically specific for residual solvents[18].

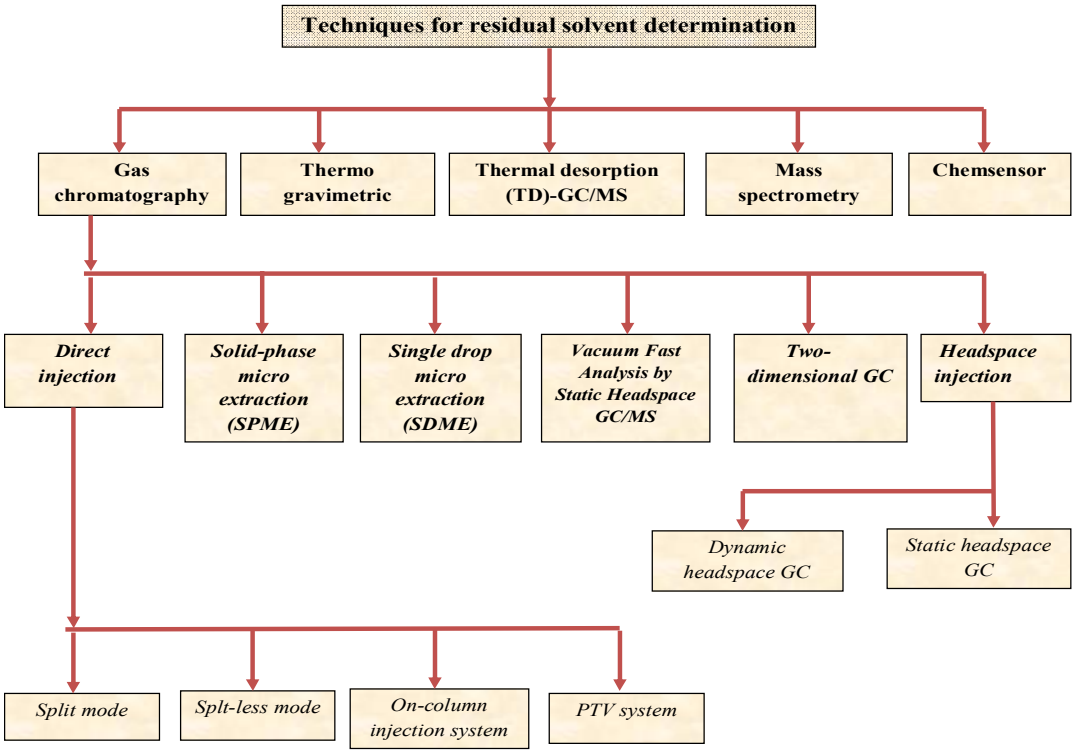

Fig 1: List of the analytical techniques used for analysis of residual solvents in pharmaceuticals.Gas liquid chromatography (GLC)

Gas liquid chromatography (GLC) techniques dominate the analytical methods for residual solvents determinations because of the volatility of organic solvents and the substantial separating capability of capillary columns.Flame ionization detector is mostly used in GLC for residual solvent determinations. However, different aspects of GLC have to be considered, like injection systems, columns, and/or detectors. Gas chromatography methods for residual solvents can be carried out either by direct injection method, headspace analysis, solid phase micro extraction (SPME) method and single drop micro extraction (SDME). The choice of injection system is determined by the sample type, the types of analytes, their quantity levels and available lab equipment.

Direct injection method

In direct injection gas chromatography, actual drug substance or formulation is injected into a GC system. The drug substance is usually dissolved in an appropriate solvent and loaded into a syringe and injected. This method is often preferred because of its simplicity and reliability. but at the same time sample matrices may contain non-volatile or corrosive substances, which may lead to the deterioration of the column. Different variants of direct injection systems are also available with variable sensitivity like split, split-less, on-column and programmed temperature vaporizing (PTV).

Headspace Injection

This technique overcomes the disadvantages associated with direct injection method and can be used for non-volatile or corrosive substances also. In headspace analysis, a continuous flow of gas is swept over the surface of a sample matrix. Volatiles from the sample matrix are conveyed into a trap where the volatile residual solvents are accumulated prior to analysis. Two types of headspace-sampling techniques are available including dynamic headspace analysis (sometimes referred to trap-and-purge analysis) and static headspace analysis having variable sensitivity.

Solid-phase micro extraction (SPME)

In SPME, a silica fiber coated with a sorbent is used to collect and concentrate the volatile solvents[25]. 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 and analyzed. The selectivity of the fiber can be modified by changing the phase type or thickness according to the characteristics of the analytes.

Single drop micro extraction (SDME)

This technique is also known as liquid micro extraction (LME). It uses a small volume of solvent suspended as a drop at the end of the micro syringe needle in the headspace phase over the sample solution. A drop size is preferred to be in the range 1 n 3 μL[26]. 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.

Two- dimensional Gas Chromatography

Two- dimensional Gas Chromatography (GC×GC) involves two columns, coupled in series by a modulating device that focuses the effluent from the first column and injects it into a second column of differing selectivity. This system employs a two-stage modulator whose timing is critical for effective second-dimension separations. With this system, the first dimension effluent is focused at the head of the second column with a jet of cryogenically cooled nitrogen gas.

This band is then heated with a jet of hot nitrogen while a second band is simultaneously focused with a cryogenically cooled liquid nitrogen pulse. This cycle is repeated, allowing the injection of success ive focused bands onto the second column.

Vacuum Fast Analysis by Static Headspace GC/MS

In this technique, standards and samples are analyzed by headspace GC/MS using elevated gas flows in order to shorten runtimes. The vacuum of the mass spectrometer is used to pull carrier gas through the column and eluting analytes are detected by a DSQ quadrupole mass spectrometer. This low pressure instrument is configured with a 200/200 L/sec differentially-pumped manifold so that it can more easily handle the elevated flow rate. The use of elevated carrier gas flows allows for fast quantitation of both the USP and ICH solvents.

Loss on drying (LOD)

This was the first method published in pharmacopoeia for the analysis of residual solvents. In this method, the amount of volatile components released from a sample under specific temperature or vacuum condition is determined by LOD but it suffers from the disadvantage of being non-specific, high limit of detection (about 0.1%), atmospheric humidity can affect the results and a large quantity of sample (usually 1g or more) must be used for the test.

Thermo gravimetric analysis (TGA)

The loss of volatile components from a sample when subjected to a temperature gradient is measured. In this method, a high detection limit of approximately 100ppm can be obtained using only a few mg of the sample. The disadvantage of these methods is that they do not speciate and account for the volatile components that are trapped in the lattice structure of the compound.

ChemSensor

ChemSensor 4440 by Agilent Technologies (Palo Alto, CA) is based on the headspace principle and mass spectrometric detection without chromatographic separation[31]. By using this instrument, Pena et al., 2003 developed a method for detecting and quantifying residual hexane in refined orujo oil. In this method, as no chromatographic separation is used, all the volatile constituents of the oil sample reach the detector simultaneously providing a global signal. But it is quite easy to discriminate the desired constituent from other volatiles of the oil sample because m/zvalues are characteristic of each constituent. This method is simple and provides high sample throughput in comparison to conventional HS-GC.

Thermal desorption (TD)-GC/MS

A programmed temperature pyrolyzer (double shot pyrolyzer) is applied for the TD and then sample is screened for GC/MS. This method does not require any sample pretreatment and allows very small amounts of the sample. Directly desorbed solvents from intact pharmaceuticals in the desorption cup are cryofocused at the head of a capillary column prior to GC/MS analysis. The desorption temperature is set at a point about 20^0C higher than the melting point of each sample individually and held for 3 min. This method allows rapid analysis and good repeatability for residual solvent determination.

Mass spectrometry (MS)

MS is a powerful analytical tool because it can provide valuable structural information with a high degree of specificity. The distinctive mass spectrum or fragmentation pattern acquired for each molecule makes it a definitive and effective tool for identifying unknown impurities or degradation products. Coupling

GC to MS is much more powerful than the sum of the two individual instruments[32]. The Headspace-GC/MS technique provides a means to identify unknown or unexpected residual solvents, and avoids the possibility of misidentifying residual solvents solely on retention time.

Although, the methods employed for the analysis of residual solvents in herbal extracts as well as herbal formulations are mostly similar to the methods employed for the analysis of residual solvents in synthetic drugs, there are specific limits prescribed in ICH guidelines which are used for the herbal analysis. Still, there are a few problems are encountered like influence of colors of the herbal extracts, two or more compounds appearing in the same retention time and the high cost of the analysis make the task more tough for the regulatory agencies to enforce its guidelines more effectively. The efforts are going on in this direction but till date there is no sufficient data available which can be presented in this paper.

CONCLUSION

Residual solvents are very undesirable substances when present above the permissible limits given by ICH guidelines. Herbal formulations are very prone to these solvents during their processing and hence must be controlled to desired levels.For their proper regulation, different pharmacopoeias have adopted the ICH guidelines for residual solvents but Indian pharmacopoeia is still lacking in control and identification of residual solvents in herbals as well as other pharmaceuticals. So, Indian regulatory agencies must come forward for their proper regulation in order to avoid their deleterious health effects.

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