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Determination of Residual Solvents In Bulk Drug and Formulations

Pardeep Singh*[1], Manish Sinha[1]
1.Department of Pharmaceutical chemistry, ASBASJSM College of Pharmacy, Bela, Ropar - 140001, Punjab, India.

ABSTRACT

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, karl fischer titration, Thermogravimetric analysis, Near- IR spectroscopy, Thermal desorption GC-MS, Gas chromatography, Nuclear magnetic resonance spectroscopy) that are being used to remove the residual solvents with their merits and demerits.

Keywords : Residual solvents, restricted limits,

*Corresponding Author Email: pardeeplongia90@gmail.com
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INTRODUCTION

Residual solvents are defined as organic volatile impurities that may remain in active substances, excipient, or medicinal products after processing. During the manufacturing processes, the solvents are not completely removed. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Residual solvents do not have any therapeutic effect. Therefore efforts should be made to remove them to the extent possible to meet the specifications prescribed. Depending upon the safety data and their risk to the human health, these solvents are classified as Class 1, Class 2, Class 3 and Class 4 residual solvents [2].

Class 1 solvents

These solvents are known to cause unacceptable toxicities and should be avoided in the manufacture of active pharmaceutical substances, excipients and medicinal products. However if their use is unavoidable, the restricted limits shown in table 1 should be applied [1,2].

Table 1. Restricted limits of Class I residual solvents

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

Class 2 solvents

These solvents are associated with less severe toxicity but should be limited in pharmaceutical products for the protection of consumers from potential adverse effects. Restricted limits shown in table 2 are applicable if any solvent of this class is used [1,2].

Table 2. Restricted limits of Class 2 residual solvents.

Acetonitrile	410
Solvent	**Concentration (ppm)**
Chloroform	60
Cyclohexane	3880
1,2 –Dichloroethene	1870
Dichloromethane	600
1,2- Dimethoxyethane	100
N,N-Dimethylacetanide	1090
N,N- Dimethylformamide	880
1,4- Dioxane	380
2- Etoxyethanol	160
Ethyleneglycol	620
Formamide	220

Hexane	290
Methanol	3000
2-Methoxyetanol	50
Ethylbutylketone	50
Methylcyclohexane	1180
N-Methylpyrrolidone	4840
Nitromethane	50
Pyridine	200
Sulpholane	160
Tetralin	100
Toulene	890
1,1,2- Trichloroethene	80
Xylene	2170

Class 3 solvents

These solvents are less toxic and of lower risk to human health. Nevertheless, they need to be limited by good manufacturing practices or other quality based requirements. The concentration limits of 5000 ppm would be acceptable for the solvents listed in table 3 [1,2].

Table 3. Class 3 residual solvents having restricted limit of 5000ppm

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

Class 4 solvents

These classes of solvents are those for which, no adequate toxicological data was found. These solvents are listed in table 4. [1,2]

Table 4. Solvents for which no adequate toxicological data was found

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

ANALYTICAL TECHNIQUES FOR THE DETERMINATION OF RESIDUAL SOLVENTS.

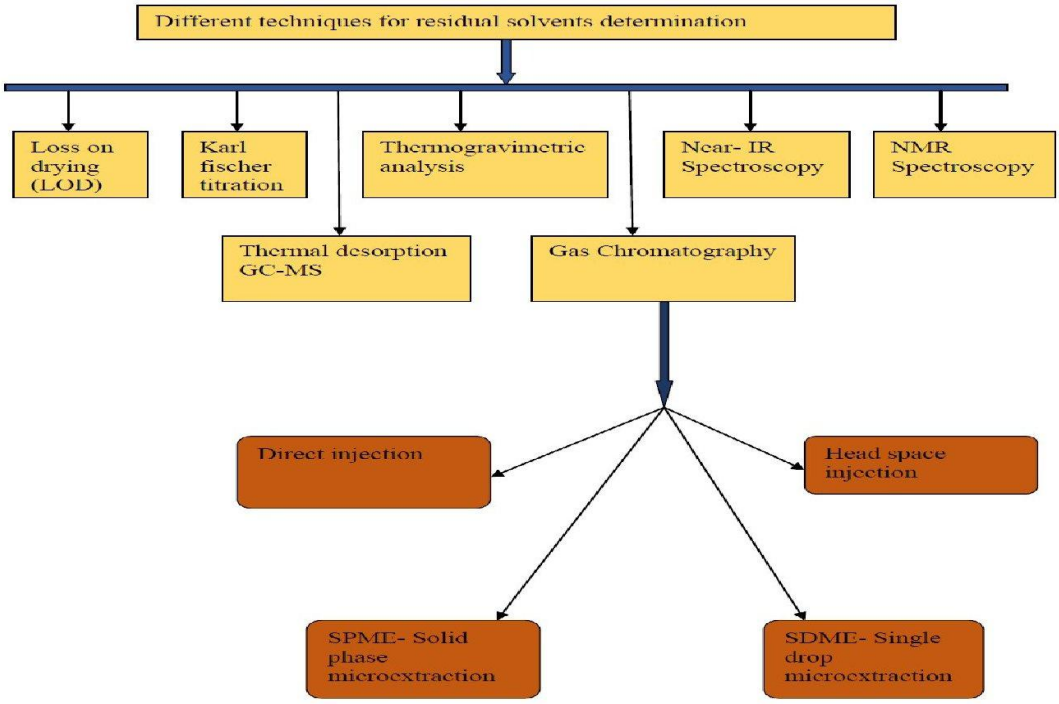

Figure 1. Anlytical techniques for the determination of residual solvents

Loss on Drying

The loss on drying technique is largely used in pharmaceutical laboratories to determine the total amount of volatiles, i.e., water and residual solvents vaporized under the experimental conditions. The test is quite simple and depends only on a properly calibrated analytical balance and an oven usually programmed at 105 ºC (or a vacuum oven in case of thermolabile APIs). In metrological terms, Loss on drying has the advantage of being a gravimetric technique and consequently a primary method of measurement. It is considered a non-specific technique and may form interfering volatile components due to sample thermal degradation. Additionally, the technique may not release all the entrained solvent or tightly bound crystallization water. Other disadvantages are the large amount of sample required and the long analysis time [3,4].

Karl-Fischer Titration

The Karl Fischer (KF) reaction is based on the quantitative reaction of water with iodine (I_2) in presence of an alcohol, a base, and sulfur dioxide (SO_2), with potentiometric determination of the endpoint. The Karl Fischer method is used to determine the total water content, i.e., surface and crystallization water. For larger water amounts (1-100%), the volumetric titration (titrant added directly to the titration chamber) is the most indicated, while the coulometric titration

(iodine titrant formed in the generator electrode) is appropriate for water amounts in the order of 10-20 µg, 150-100 ppm, or few µg. Both methods can be carried out either by direct introduction of samples in the titration chamber or by using an oven that heats the sample to vaporize the water, which is then transferred to the titration cell by a stream of an inert gas.

The reaction involved in the Karl Fischer titration can be given as:

$$I_2 + SO_2 + 3Base + ROH + H_2O \longrightarrow 2Base.H^+I^- + Base.HSO_4R$$

Base: Amine, Pyridine etc.

ROH: 2-Methoxyethanol, Methanol, etc.

The KF method is highly selective to water and very reproducible. The drawback of the technique is the restriction to use the direct addition in case of analytes that are not soluble in or that react with the KF reagent, for instance thiols, aldehydes, ketones, amines, cupric salts and ferric salts [3,4].

Thermogravimetric Analysis

Thermogravimetric analysis (TGA) is another technique that can be applied to determine volatiles and is based on changes in sample weight when it is exposed to a temperature-time-program in a defined gas atmosphere. The correct assignment of the type of volatile components, namely water or residual solvent, is easier to carry out when the equipment is connected to a mass spectrometer (TGA-MS). In this technique a sample is placed into a tared TGA sample pan which is attached to a sensitive microbalance assembly. The sample holder portion of the TGA balance assembly measures the initial sample weight at room temperature and then continuously monitors changes in sample weight as heat is applied to the sample [3,4].

Advantage: The technique requires only 2-5 mg sample and can recognize the types of water binding.

Disadvantage: It require long analysis time.

Thermogravimetric analysis can provide information on physical phenomena like vaporization , sublimation, absorption, adsorption, desorption and chemical phenomena like chemisorptions, desolvation, decomposition, oxidative degradation, solid state reactions.

Near-IR Spectroscopy

The infrared spectroscopy (IR) has a high potential for identification (classification) and quantification, especially when combined to chemometric methods. It is non-destructive, requires minimum sample preparation and can be used to determine water and residual solvents. The near infrared spectroscopy (800-2500 nm or 12821-4000 cm^{-1}) was reported to be the best

method to differentiate between different water species. According to Cao *et.al.* NIR spectra at 1860-2020 nm (OH stretching and OH bending) could be deconvoluted into individual spectra corresponding to hydrate and surface water of mannitol [3,4].

Table 5. Solvent peaks in Infra Red Spectroscopy [6]

	Type of vibration	Frequency(cm^{-1})	Intensity
C-H	Alkanes (strecth)	3000-2850	s
	CH3 (bend)	1450-1375	m
	CH2(bend)	1465	m
	Alkenes (strecth)	3100-3000	m
	(out of plane bend)	1000-650	s
	Aromatics (strecth)	900-690	s
	(out of plane bend)	3150-3050	s
	Alkyne(strecth)	Ca. 3300	s
	Aldehyde	2900-2800	w
		2800-2700	w
C-C	Alkane	Not interpretatively useful	
C=C	Alkene	1680-1600	m-w
	Aromatic	1600and 1475	m-w
CΞC	Alkyne	2250-2100	m-w
C=0	Aldehyde	1740-1720	s
	Ketone	1725-1705	s
	Carboxylic acid	1725-1700	s
	Ester	1750-1730	s
	Amide	1680-1630	s
	Anhydride	1800 and 1760	s
	Acid chloride	1800	s
C-O	Alcohols, ethers, esters, carboxylic acids, anhydrides	1300-1000	s
O-H	Alcohols, phenols Free	3650-3600	m
	H-bonded	3400-3200	m
	Carboxylic acids	3400-2400	m
N-H	Primary and secondary amines and amides		
	(strecth)	3500-3100	m
	(bend)	1640-1550	m-s
C-N	Amines	1350-1000	m-s
C=N	Imines and Oximes	1690-1640	w-s
CΞN	Nitriles	2260-2240	m
X=C=Y	Allenes, Ketenes, isocyanates, isothiocynates	2270-1940	m-s
N=O	Nitro(R-NO_2)	1550 and 1350	s
S-H	Mercaptanes	2550	w
S=O	Sulfoxides	1050	s
C-X	Sulfones, sulfonyl chlorides, sulfates, sulfonamides	1375-1300 and 1350-1140	s
	Fluoride	1400-1000	s
	Chloride	785-540	s
	Bromide, iodide	<647	s

Disadvantage: The main drawback of IR Spectroscopy is its low sensitivity, usually above 100 ppm or 1% concentration.

The various solvent peaks in IR spectra are listed in the table 5.

NMR-Spectroscopy

The nuclear magnetic resonance can be used for screening and identification of residual solvents. However, NMR is reported to have high detection limits, and may not be sufficiently sensitive to determine water and residual solvents in pharmaceuticals. Additionally, the water present in deutrated solvents may be taken into account [3,4] .

Parrick A. Hays, *et.al.* (2005) developed a proton nuclear magnetic resonance spectroscopy (NMR) methods for determining the purity of reference drug standards and illicit forensic drug seizures. The methodology uses a weighed sample dissolved in a deuterated solvent or solvent mixture containing a high purity internal standard. The NMR experiment employs 8 scans using a 45 second delay and 90◦ pulse. In the determination of purity of reference standards, the number of quantitative determinations available is equal to the number of peak groups that are baseline resolved. The relative standard deviation (RSD) of these signals is usually <1% for pure standards, and the results agree well with other purity determining methods. This method can also aid in the determination of correct molecular weight for standards containing an unknown number of waters of hydration or an unknown number of acids per drug in salts. In the presented study, the linearity of the NMR probe was determined using methamphetamine HCl dissolved in deuterium oxide (D2O) with maleic acid as the internal standard (5 mg) for a range of concentrations from 0.033 to 69.18 mg/ml with a resulting correlation coefficient of >0.9999 for all 6 methamphetamine peak groups. The spectra of complex illicit heroin, methamphetamine, MDMA, and cocaine samples are presented, as well as an extensive list of compounds, their solubilities and the solvent(s) and internal standard used.

NMR SOLVENT STORAGE ANDHANDLING INFORMATION

Acetic Acid-d4 / Acetone-d6 / Benzene-d6 / Cyclohexane-d12 / Deuterium Oxide / N,N-Dimethylformamide-d7 / Dimethyl Sulfoxide-d6 /1,4-Dioxane-d8 (p-Dioxane) / Ethanol-d6 / Methanol-d4 / Methylene Chloride-d2 / Pyridine-d5 / 1,1,2,2 Tetrachloroethane-d2 / Toluene-d8 / Trifluoroacetic Acid-d / 2,2,2-Trifluoroethanol-d3 Store at room temperature away from light and moisture. The above products are stable if stored under recommended conditions.

Acetonitrile-d3

Store at room temperature away from light and moisture. This product is stable for one year after receipt of order if stored under above conditions (unopened). After one year, the solvent should be re-analyzed for chemical purity before use.

Chloroform-d / Tetrahydrofuran-d8

Store refrigerated (-5o to 5oC) away from light and moisture. These products are stable for six months after receipt of order if stored under above conditions (unopened). After six months, the solvent should be re-analyzed for chemical purity before use

Gas Chromatography

GC methods have been developed to monitor residual solvents in pharmaceutical products routinely. The most popular techniques of sample introduction into the gas chromatograph include direct injection, static or dynamic headspace, solid-phase microextraction and single drop microextraction. In gas Chromatography various solvent peaks appeared at different t_r (Retention times) in the graph. Based on the area of the peaks, concentration of the solvents in sample is calculated. In conclusions, gas chromatography-based procedures were described as the most appropriate because of the lowest detection limits, ease of sample preparation and specificity [5].

Farajzadeh M.A, *et.al* (2012) developed a Dispersive liquid-liquid microextraction combined with gas chromatography for extraction and determination of class 1 residual solvents in pharmaceuticals. Solvents of high boiling point were selected as dispersive and extraction solvents in order to prevent their chromatographic peaks from overlapping with those of analytes that have short retention times. They have taken 500 mg samples, limit of detections for the tested pharmaceuticals were obtained as 0.11, 0.03, 0.05, 0.05, and 0.006 µg g(-1) for 1,1-chloroethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane and benzene respectively, which are considerably much lower than their permissible limits in pharmaceuticals [9].

Katarzyna Grodowska, *et.al.* (2010) developed an analytical method for Residual solvents determination in pharmaceutical products. A 30m X 0.32mm column coated with 3.0µm layer of phase G43IV with a 5m X 0.53mm guard column deactivated with phenylmethyl siloxane phase with FID detector. Helium was used as a carrier gas, the detector temperature was kept at 250ºC. This test was performed for confirmation that benzene, methylene chloride, trichloroethylene, 1,4-dioxane and chloroform are below maximum acceptable limits 10.

Table 6. NMR Solvent data chart[7]

	^{1}H Chemical shift(ppm from TMS multiplicity)	**JCD (H_Z)**	**^{13}C Chemical shift(ppm from TMS multiplicity)**	**JCD (H_Z)**	**^{1}H Chemical shift of HOD (ppm from TMS)**	**Density at 20°C**	**Melting point(° C)**	**Boiling point (°C)**	**Dielectric constant**	**MW**
acetic acid-d_4	11.65 (1) 2.04 (5)	2.2	178.99 (1) 20.0 (7)	20	11.5	1.12	16.7	118	6.1	64.08
acetone-d_6	2.05 (5)	2.2	206.68 (1) 29.92 (7)	0.9 19.4	2.8 *	0.87	-94 5	6.5	20.7	64.12
acetonitrile-d_3	1.94 (5)	2.5	118.69 (1) 1.39 (7)	21	2.1 *	0.84	-45	81.6	37.5	44.07
benzene-d_6	7.16 (1)		128.39 (3)	24.3	0.4	0.95	5.5	80.1	2.3	84.15
chloroform-d	7.24 (1)		77.23 (3)	32.0	1.5 *	1.50	-63.5	61-62	4.8	120.38
cyclohexane-d_{12}	1.38 (1)		26.43 (5)	19	0.8	0.89	6.47	80.7	2.0	96.24
deuterium oxide	4.80 (DSS) 4.81 (TSP)		NA	NA	4.8	1.11	3.81	101.42	78.5	20.03
n, n-dimethyl-formamide-d_7	8.03 (1)		163.15 (3)	29.4	3.5	1.03	-61	153	36.7	80.14
	2.92 (5)	1.9	34.89 (7)	21.0						
	2.75 (5)	1.9	29.76 (7)	21.1						
dimethyl sulfoxide-d_6	2.50 (5)	1.9	39.51 (7)	21.0	3.3 *	1.19	18.45	189	46.7	84.17
1,4-dioxane-d_8	3.53 (m)		66.66 (5)	21.9	2.4	1.13	11.8	101.1	2.2	96.16
ethanol-d_6	5.19 (1)				5.3	0.89 1	-114.1	78.5	24.5	52.1
	3.56 (1)		56.96 (5)	22						
	1.11 (m)		17.31 (7)	19						
methanol-d_4	4.78 (1)				4.9	0.89	-97.8	64.7	32.7	36.07
	3.31 (5)	1.7	49.15 (7)	27.2						
methylene chloride-d_2	5.32 (3)	1.1	54.00 (5)	27.5	1.5	1.35	-95	39.75	8.9	86.95
pyridine-d_5	8.74 (1)		150.35 (3)	24.5	5	1.05	-42	115-116	12.4	84.13
	7.58 (1)		135.91 (3)	25						
	7.22 (1)		123.87 (3)							
1,1,2,2-	6.0		73.78 (3)							

tetrachloroethane-d_2										
tetrahydrofuran-d_8	3.58 (1)		67.57 (5)	22.2		1.62	-44	147	8.20	169.86
	1.73 (1)		25.37 (5)	20.2	2.4-2.5	0.99	-108.5	66	7.6	80.16
toluene-d_8			137.86 (1)		0.4	0.94	-95	110.6	2.4	100.19
	7.09 (m)		129.24 (3)	23						
	7.00 (1)		128.33 (3)	24						
	6.98 (5)		125.49 (3)	24						
	2.09 (5)	2.3	20.4 (7)	19						
trifluoroacetic acid-d	11.50 (1)		164.2 (4)		11.5	1.41	-15.4	72.4		115.03
			116.6 (4)							
trifluoroethanol-d_3	5.02 (1)		126.3 (4)		5	1.41	-43.3	75		103.06
	3.88 (4x3)	2(9)	61.5 (4x5)	22						

The ^{1}H and ^{13}C NMR chemical shifts of some common laboratory solvents is given in the table 5 and 6 respectively. The NMR spectra were taken in a Bruker DPX-300 instrument (300.1 and 75.5 MHz for ^{1}H and ^{13}C respectively) [6].

Table 5. ^{1}H NMR Data[8]

	Proton	**mult**	**$CDcl_3$**	**$(CD_3)_2CO$**	**$(CD_3)_2SO$**	**C_6D_6**	**CD_3CN**	**CD_3OD**	**D_2O**
Solvent residual peak			7.26	2.05	7.16	1.94	1.94	3.31	4.79
H_2O		s	1.56	2.84[a]	3.33[a]	0.40	2.13	4.87	
acetic acid	CH_3	s	2.10	1.96	1.91	1.55	1.96	1.99	2.08
acetone	CH_3	s	2.17	2.09	2.09	1.55	2.08	2.15	2.22
acetonitrile	CH_3	s	2.10	2.05	2.07	1.55	1.96	2.03	2.06
benzene	CH	s	7.36	7.36	7.37	7.15	7.37	7.33	
tert- butyl alcohol	CH_3	s	1.28	1.18	1.11	1.05	1.16	1.40	1.24
	OH[C]	s			4.19	1.55	2.18		
tert-butyl methyl ether	CCH_3	s	1.19	1.13	1.11	1.07	1.14	1.15	1.21
	OCH_3	s	3.22	3.13	4.19	3.04	3.13	3.20	3.22
BHT[b]	ArH	s	6.98	6.96	1.11	7.05	6.97	6.92	
	OH[c]	s	5.01		3.08	4.79	5.20		
	$ArCH_3$	s	2.27	2.22	6.87	2.24	2.22	2.21	
	$ArC(CH_3)_3$	s	1.43	1.41	6.65	1.38	1.34	1.40	
chloroform	CH	s	7.26	8.02	2.18	6.15	7.58	7.90	
cyclohexane	CH_2	s	1.43	1.43	1.36	1.40	1.44	1.45	

1,2- dichloromethane	CH_2	s	3.73	3.87	8.32	2.90	3.81	3.78	
dichloromethane	CH_2	s	5.30	5.63	1.40	4.27	5.44	5.49	
diethyl ether	CH_3	t,*7*	1.21	1.11	3.90	1.11	1.12	1.18	1.17
	CH_2	q,*7*	3.48	3.41	5.76	3.26	3.42	3.49	3.56
diglyme	CH_2	m	3.65	3.56	1.09	3.46	3.53	3.61	3.67
	CH_2	m	3.57	3.47	3.38	3.34	3.45	3.58	3.61
	OCH_3	s	3.39	3.28	3.24	3.11	3.29	3.35	3.37
1,2-dimethoxyethane	CH_3	s	3.40	3.28	3.24	3.12	3.28	3.35	3.37
	CH_2	s	3.55	3.46	3.43	3.33	3.45	3.52	3.60
dimethylacetamide	CH_3CO	s	2.09	1.97	1.96	1.60	1.97	2.07	2.08
	N CH_3	s	3.02	3.00	2.94	2.57	2.96	3.31	3.06
	N CH_3	s	2.94	2.83	2.78	2.05	2.83	2.92	2.90
dimethylforamide	CH	s	8.02	7.96	2.95	7.63	7.92	7.97	7.92
	CH_3	s	2.96	2.94	2.89	2.36	2.89	2.99	3.01
	CH_3	s	2.88	2.78	2.73	1.86	2.77	2.86	2.85
dimethyl sulfoxide	CH_3	s	2.62	2.52	2.54	1.68	2.50	2.65	2.71
dioxane	CH_2	s	3.71	3.59	3.57	3.35	3.60	3.66	3.75
ethanol	CH_3	t,7	1.25	1.12	1.06	0.96	1.12	1.19	3.65
	CH_2	q,7[d]	3.72	3.57	3.44	3.34	3.54	3.60	
	OH	s[c,d]	1.32	3.39	4.63		2.47		2.07
ethyl acetate	CH_3 CO	s	2.05	1.97	1.99	1.65	1.97	2.01	4.14
	CH_2 CH_3	q,7	4.12	4.05	4.03	3.89	4.06	4.09	1.24
	CH_2 CH_3	t,7	1.26	1.20	1.17	0.92	1.20	1.24	2.19
ethyl methyl ketone	CH_3 CO	s	2.14	2.07	2.07	1.58	2.06	2.12	3.18
	CH_2 CH_3	q,7	2.46	2.45	2.43	1.81	2.43	2.50	2.16
	CH_2 CH_3	t,7	1.06	0.96	0.91	0.85	0.96	1.01	3.65
ethylene glycol	CH	s[e]	3.76	3.28	3.34	3.41	3.51	3.59	
"grease"[f]	CH_3	m	0.86	0.87		0.92	0.86	0.88	
	CH_2	br s	1.26	1.29		1.36	1.27	1.29	
n-hexane	CH_3	t	0.88	0.88	0.86	0.89	0.89	0.90	
	CH_2	m	1.26	1.28	1.25	1.24	1.28	1.29	
HMPA[g]	CH_3	d,9.5	2.65	2.59	2.53	2.40	2.57	2.64	2.61
methanol	CH_3	s[h]	3.49	3.31	3.16	3.07	3.28	3.34	3.34

	OH	s[c,h]	1.09	3.12	4.01		2.16		
nitromethane	CH_3	s	4.33	4.43	4.42	2.94	4.37	4.34	4.40
n-pentane	CH_3	t,7	0.88	0.88	0.86	0.87	0.89	0.90	
	CH_2	m	1.27	1.27	1.27	1.23	1.29	1.29	
2-propanol	CH_3	d,6	1.22	1.10	1.04	0.85	1.09	1.50	1.17
	CH	sep,6	4.04	3.90	3.78	3.67	3.87	3.92	4.02
pyridine	CH(2)	m	8.62	8.58	8.58	8.53	8.57	8.53	8.52
	CH(3)	m	7.29	7.35	7.39	6.66	7.33	7.44	7.45
	CH(4)	m	7.68	7.76	7.79	6.98	7.73	7.85	7.87
silicone grease	CH_3	s	0.07	0.13		0.29	0.08	0.10	0.88
tetrahydrofuran	CH_2	m	1.85	1079	1.76	1.40	1.80	1.87	3.74
	CH_2O	m	3.76	3.63	3.60	3.57	3.64	3.71	
toluene	CH_3	s	2.36	2.32	2.30	2.11	2.33	2.32	
	CH(*o/p*)	m	7.17	7.1-7.2	7.18	7.02	7.1-7.3	7.16	
	CH(*m*)	m	7.25	7.1-7.2	7.25	7.13	7.1-7.3	7.16	
triethylamine	CH_3	t,7	1.03	0.96	0.93	0.96	0.96	1.05	0.99
	CH_2	q,7	2.53	2.45	2.43	2.40	2.45	2.58	2.57

Table 6. ^{13}C NMR Data [8]

		$CDcl_3$	**$(CD_3)_2CO$**	**$(CD_3)_2SO$**	**C_6D_6**	**CD_3CN**	**CD_3OD**	**D_2O**
Solvent residual peak		77.160.06	29.84±0.1	39.52±0.06	128±0.02	1.32±0.02	49.0±0.01	
			206.26±0.13			118.23±0.02		
acetic acid	CO	175.99	172.31	171.93	175.82	173.21	175.11	177.21
	CH_3	20.81	20.51	20.51	20.37	20.73	20.56	21.03
acetone	CO	207.07	205.87	206.31	204.43	207.43	209.67	25.94
	CH_3	30.92	30.60	30.56	30.14	30.91	30.67	30.89
acetonitrile	CN	116.43	117.60	117.91	116.02	118.26	118.06	119.68
	CH_3	1.89	1.12	1.03	0.20	1.79	0.85	1.47
benzene	CH	128.37	129.15	128.30	128.62	129.32	129.34	70.36
tert- butyl alcohol	C	69.15	68.13	66.88	68.19	68.74	69.40	30.29
	CH_3	31.25	30.72	30.38	30.47	30.68	30.91	49.37
tert-butyl methyl ether	OCH_3	49.45	49.35	48.70	19.19	49.52	49.66	75.62
	C	72.87	72.81	72.04	72.40	73.17	74.32	26.60
	CCH_3	26.99	27.24	26.79	27.09	27.28	27.22	

BHT	C(1)	151.55	152.51	151.47	152.05	152.42	152.85	
	C(2)	135.87	138.19	139.12	136.08	138.13	139.09	
	CH(3)	125.55	129.05	127.97	128.52	129.61	129.49	
	C(4)	128.27	126.03	124.85	125.83	126.38	126.11	
	CH_3Ar	21.20	21.31	20.97	21.40	21.23	21.38	
	CH_3C	30.33	35.00	31.25	31.34	31.50	31.15	
	C	39.25	31.61	34.33	34.55	35.05	35.36	
chloroform	CH	77.36	79.19	79.16	77.79	79.17	79.44	
cyclohexane	CH_2	26.94	27.51	26.33	27.23	27.63	27.96	
1,2- dichloromethane	CH_2	43.50	45.25	45.02	43.59	45.54	45.11	
dichloromethane	CH_2	53.52	54.95	54.84	53.46	55.32	54.78	
diethyl ether	CH_3	15.20	15.78	15.12	15.46	15.63	15.46	14.77
	CH_2	65.91	66.12	62.05	65.94	66.32	66.88	66.42
diglyme	CH_3	59.01	58.77	57.98	58.66	58.90	59.06	58.67
	CH_2	70.51	71.03	69.54	70.99	70.99	71.33	70.05
	CH_2	71.90	72.63	71.25	72.35	72.63	72.92	71.63
1,2-dimethoxyethane	CH_3	59.08	58.45	58.01	58.68	58.89	59.06	58.67
	CH_2	71.84	72.47	17.07	72.21	72.47	72.72	71.49
dimethylacetamide	CH_3	21.53	21.51	21.29	21.16	21.76	21.32	21.09
	CO	171.07	170.61	169.54	169.95	171.31	173.32	174.57
	N CH_3	35.28	34.89	37.38	34.67	35.17	35.50	35.03
	N CH_3	38.13	37.92	34.42	37.03	38.26	38.43	38.76
dimethylforamide	CH	162.62	162.79	162.29	162.13	163.31	164.73	165.53
	CH_3	36.50	36.15	35.73	35.25	36.57	36.89	37.54
	CH_3	31.45	31.03	30.73	30.72	31.32	31.61	32.03
dimethyl sulfoxide	CH_3	40.76	41.23	40.45	40.03	41.31	40.45	39.39
dioxane	CH_2	67.14	67.60	66.36	67.16	67.72	68.11	67.19
ethanol	CH_3	18.41	18.89	18.57	18.72	18.80	18.40	17.47
	CH_2	58.28	57.72	56.07	57.86	57.96	58.26	58.05
ethyl acetate	CH_3 CO	21.04	20.83	20.68	20.56	21.16	20.88	21.15
	CO	171.36	170.96	170.31	170.44	171.68	172.89	175.26
	CH_2	60.49	60.56	59.74	60.21	60.98	61.50	62.32
	CH_3	14.19	14.50	14.40	14.19	14.54	14.49	13.92

ethyl methyl ketone	CH_3CO	29.49	29.30	29.26	28.56	29.60	29.39	29.49
	CO	209.56	208.30	208.72	206.55	209.88	212.16	218.43
	CH_2 CH_3	36.89	36.75	35.83	36.36	37.09	37.34	37.27
	CH_2 CH_3	7.86	8.03	7.61	7.91	8.14	8.09	7.87
ethylene glycol	CH_2	63.79	64.26	62.76	64.34	64.22	64.30	63.17
"grease"[f]	CH_2	29.76	30.73	29.26	30.21	30.86	31.29	
n-hexane	CH_3	14.14	14.34	13.88	14.32	14.43	14.45	
	CH_2(2)	22.70	23.28	22.05	23.04	23.40	23.68	
	CH_2(3)	31.64	32.30	30.95	31.96	32.36	32.73	
HMPA[g]	CH_3	36.87	37.04	36.42	36.88	37.10	37.00	
methanol	CH_3	50.41	49.77	48.59	49.97	49.90	48.86	36.46
nitromethane	CH_3	62.50	63.21	63.28	61.16	63.66	63.08	49.50
n-pentane	CH_3	14.08	14.29	13.18	14.25	14.37	14.39	63.22
	CH_2(2)	22.38	22.98	21.70	22.72	23.08	23.38	
	CH_2(3)	34.16	34.83	33.48	34.45	34.89	35.30	
2-propanol	CH_3	25.14	25.67	25.43	25.18	25.55	25.37	24.38
	CH	64.50	63.85	64.92	64.23	64.30	64.71	64.88
pyridine	CH(2)	149.90	150.67	149.58	150.27	150.76	150.07	149.18
	CH(3)	123.75	124.57	123.84	123.58	127.76	125.53	125.12
	CH(4)	135.96	136.56	136.05	135.28	136.89	138.35	138.27
silicone grease	CH_3	1.04	1.40	25.14	1.38	26.27	2.10	
tetrahydrofuran	CH_2	25.62	26.15	67.03	25.72		26.48	25.67
	CH_2O	67.97	68.07	20.99	67.80	68.33	68.83	68.68
toluene	CH_3	21.46	21.46	137.35	21.10	21.50	21.50	
	C(i)	137.89	138.48	128.88	137.91	138.90	138.85	
	CH(*o*)	129.07	129.76	128.18	129.33	129.94	129.91	
	CH(*m*)	128.26	129.03	125.29	128.56	129.23	129.20	
	CH(*p*)	125.33	126.12	11.74	125.68	126.28	126.29	
triethylamine	CH_3	11.61	12.49	45.74	12.35	12.38	11.09	9.07
	CH_2	46.25	47.07		46.77	47.10	46.96	47.19

Cheng C, *et.al.* (2010) developed a generic static headspace gas chromatography method for determination of residual solvents in drug substance. 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. The two-stage gradient GC run from 35 to 240°C, using an Agilent DB-624 capillary column (30 m long, 0.32 mm I.D, 1.8 μm film thickness). This method was suitable to determine 44 ICH classes 2 and 3 solvents in 30 min. The recoveries of most of these solvents from four drug substances are greater than 80% within the method determination ranges [11].

Perez Pavon J.L, et.al. (2007) developed Analysis of class 1 residual solvents in pharmaceuticals using headspace programmed temperature vaporization fast gas chromatography-mass spectrometry. The applicability of a headspace (HS) autosampler in combination with GC equipped with a programmed temperature vaporizer (PTV) and a MS detector was explored. Different injection techniques were compared. The benefits of using solvent injection instead of split or splitless-hot injection for the measurement of volatile compounds are shown: better peak shapes, better signal-to-noise ratios, and hence better detection limits. The proposed method was extremely sensitive. The limits of detection ranged from 4.9 ppt (benzene) to 7.9 ppt (1,2-dichloroethane) and precision was equal to or lower than 12% in all cases[12].

Camarasu C.C, *et.al.* (1998) carried out residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME. Three fibres with different polymer films were compared and the polydimethylsiloxane/divinylbenzene coated fiber was found to be the most sensitive for the analyzed analytes. Between the investigated sample preparation techniques, gas tight-SPME proved to be the most sensitive, with DL values ranging from 5 pg ml(-1) to 2 ng ml(-1). Headspace SPME was more precise, with RSD of peak areas values ranging from 2 to 3%. The headspace SPME method was successfully validated. The most important difference between the two techniques is that the gastight SPME showed better behavior towards very volatile solvents. Compared with the static headspace technique, both SPME methods showed superior results, being compatible with the pharmaceutical samples [13].

REGULATIONS FOR RESIDUAL SOLVENTS

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 pharmaceuticals. These guidelines recommened 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 (HEC) and the integrated risk Information System (IRIS) monographs [14].

CONCLUSION

Solvents are being used in almost every step of the elaboration of a drug product. Their residues could be detrimental for the processability and stability of the pharmaceutical products and the safety of patients. The testing and control of Residual solvents has been thoroughly assessed and is based on robust and sensitive techniques. After studying the different techniques of residual solvent determination it was found that Gas chromatography offers greater sensitivity, accuracy and robustness over all the other analytical techniques.

REFERENCES

1. Government of India. Ministry of health and family welfare. Indian Pharmacopoeia Vol. I. The Controller of Publication, New Delhi; 2010: 650-656.
2. Government of Great Britain. British pharmacopeia commission, London. Vol. 1. London 2009: 913-915.
3. Nogueira R, Suzane M, Gisele E, Silva B, Werickson F, Rocha C. Determination of Volatiles in pharmaceutical certified reference materials. J. Braz Chem Soc. 2012; 23: 1636-1646.
4. Katarzyna G, Andrzej P. Analytical methods for residual solvents determination in pharmaceutical products. Polish Pharmaceutical Society Drug Research. 2010; 67: 13-26.
5. Reddy PB, Reddy MS. Residual solvents determination by HS-GC with flame ionization detector in Omeprazole pharmaceutical formulations. Int J. Pharma Tech Research. 2009; 1: 230-234.
6. Pavia LD, Lampman MA, Kriz SG, Vyvyan RJ. Spectroscopy. Cengage learning private India limited, 2007: 38.
7. Budavari S, Neil MJ, Smith A, Heckelman PE. The Merck Index, an Encyclopedia of Chemicals, Drugs, and Biologicals - Eleventh Edition, Merck Co., Inc. Rahway, NJ. 1989.
8. Gottlieb HE, Kotlyar V, Nudelman A. NMR Chemical shifts of Common laboratory solvents as trace impurities. J. Org. Chem. 1997; 62: 7512-7515.
9. Farajzadeh MA, Goushjuii L, Djozan D, Mohammadi JK. Dispersive liquid-liquid microextraction combined with gas chromatography for extraction and determination of

class 1 residual Solvents in pharmaceuticals. J. Sep Sci. 2012; 35(8): 1027-1035.

10. Katarzyna G, Parczewski A. Analytical methods for residual solvents determination in pharmaceutical products. Polish Pharmaceutical Society Drug Research. 2010; 67: 13-26.
11. Cheng C, Liu S, Mueller BJ, Yan Z. A generic static headspace gas chromatography method for determination of residual solvents in drug substance. J. Chromatography A. 2010; Oct 8: 1217, (41): 6413-6421.
12. Perez PJL, Del NSM, Fernández LMA, García PC, Moreno CB. Analysis of class 1 residual solvents in pharmaceuticals using headspace-programmed temperature vaporization-fast gas chromatography-mass spectrometry. J. Chromatogr A. 2007; Feb 2, 1141(1): 123-30.
13. Camarasu CC, Mezei SM, Varga GB. Residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME. J. Pharm Biomed Anal. 1998; Dec, 18(4-5): 623-38.
14. Solanki J, Mehta M, Satija S, Garg M. Regulatory and analytical aspects of residual solvents in Ayurvedic formulations-A recent update. Int J. Res Reviews in Pharm Applied science. 2012; 2(5): 938-949.