Organic Volatile Impurities in Pharmaceuticals

S. B. PURANIK*, P. N. S. PAI AND G. K. RAO
Department of Quality Assurance, Al-Ameen College of Pharmacy, Bangalore - 560 027, India

Organic volatile impurities are residual solvents that are used in and are produced during the synthesis of drug substances, or in excipients used in the production of drug formulations. Many of these residual solvents generally cannot be completely removed by standard manufacturing processes or techniques and are left behind, preferably at low levels.

Key words: Gas chromatography, Residual solvents, Organic volatile impurities

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. Furthermore, the determination of polar residual solvents in pharmaceutical preparations continues to present an analytical challenge mainly because these compounds are quite difficult to remove from water or polar solvents. Organic impurities[1-3] 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 drugs substance, 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. 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 individual. OVI's also affect physico-chemical properties of the bulk drug substances. Crystallinity[4-7] of the bulk drug can be affected, as difference in the crystal structure of the bulk drug may lead to change in dissolution properties and problems with formulations of the finished product. Finally, residual solvents can create odor problem and color changes in the finished products.

***For correspondence**
E-mail: sangpur@rediffmail.com

Scope:

Residual solvents in drug substances, excipients and drug products fall in the scope of ICH guidelines[3], 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 levels in the 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. 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 30days) or topical application, with proper justification made on case-by-case basis.

Toxicity of residual solvents in pharmaceuticals:

Exposure limits in guideline[3] 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 assumption 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 organization for Economic co-operation and Development (OECD) and the US Food and Drug Administration (FDA) Red Book.

As per ICH Guidelines[2,8] 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 tetrachloride (4), 1,1-dichloroethane (8), 1,2-dichloroethane (5), and 1,1,1-trichloroethane (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 in Table 1.

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, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene, dimethyl sulfoxide (DMSO), ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propranol, pentene, 1-pentanol, 1-propanol, 2-propanol, propyl acetate and tetrahydrofuran.

TABLE 1: CLASS 2 SOLVENTS WITH THEIR PERMISSIBLE DAILY EXPOSURE LIMITS[1]

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

No adequate toxicological data is available for solvents classified as class 4 solvents. These solvents are 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methylisopropyl ketone, methyltetrahydrofuran, petroleum ether, trichloroacetic acid and trifluoroacetic acid. 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.

Limits for residual solvent levels:

The International Conference on Harmonization of Technical requirements for registration of pharmaceuticals for human use (ICH) has adopted Impurities Guidelines Residual Solvents, which prescribe limits for the content of solvents which may remain in new active substances, excipients and medicinal products after processing. The European Pharmacopoeia applies the same principles enshrined in the guidelines to existing active substances,

excipients and medicinal products whether or not they are the subject of a monograph of the Pharmacopoeia. All substances and products are to be tested for the content of solvents likely to be present in a substances or products. If the use of a class 1 solvent has been justified and authorized, then it is to be limited in the test section of the individual monograph. Normally monographs of the pharmacopoeia will not include limit test for individual solvents belonging to class 2 since the solvents employed may vary from one manufacturer to another. Therefore, the competent authority is to be informed of the solvents employed during the production process. This information is also to be given in the dossier submitted for a certificate of suitability and is mentioned on the certificate. When only class 3 solvents are used in the production process, a loss on drying test may be applied. If a class 3 solvent has a limit greater than 0.5 percent, which is justified and authorized, a specific determination of that solvent is required. In this case, the limit is to be given in the individual monograph, as the definition refers to the water free and solvent free substances. In all cases, the competent authority is to be informed of the solvents employed. As for class 2, this information is to be mentioned in the certification of suitability.

METHODS FOR ORGANIC VOLATILE IMPURITY (OVI) ANALYSIS

The OVI analyses include loss on drying (LOD), thermo gravimetric analysis (TGA), spectroscopic and spectrometric methods and gas chromatographic methods. Solvents that are analyzed using some of these methods have been listed in Tables 2-8.

Loss on drying (LOD)[7]:

In this method, the amount of volatile components released from a sample under specific temperature or vaccum condition is determined by loss on drying. LOD suffers from the main disadvantage of being nonspecific. Two 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 1 g or more of the material is used for a typical test to achieve a detection limit of 0.1% (w/w) or less.

Thermogravimetric analysis (TGA)[2]:

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 components that are trapped in the lattice structure of the compound. A detection limit of approximately 100 ppm can be obtained, using only a few mg of the sample.

TABLE 2: THERMOGRAVIMETRIC ANALYSIS: A DETECTION LIMIT OF 100 PPM CAN BE OBTAINED USING ONLY A FEW MILLIGRAM OF THE SAMPLE.

Solvents	ICH Q3C class	ppm limit according to ICH
Methylenechloride	2	600
Chloroform	2	60

TABLE 3: SPECTROSCOPIC AND SPECTROMETRIC METHODS: GENERALLY LACKED THE LOW DETECTION LIMITS NEDED FOR TOXIC RESIDUAL SOLVENTS[9].

Solvents	ICH Q3C class	ppm limit according to ICH
Tetrahydrofuran	2	-
Dichloromethane	2	600
Benzene	1	2
Toluene	2	890
Acetone	3	-
Ethylether	3	-

TABLE 4: DIRECT INJECTION METHOD: WATER INSOLUBLE PHARMACEUTICALS DISSOLVED IN DMSO[2].

Solvents	ICH Q3C class	ppm limit according to ICH
Methanol	2	3000
Methylene chloride	2	600
Hexane	2	290
Ethylacetate	3	-
Tetrahydrofuran	3	-
Iso-octane	4	-
1,4-dioxane	2	380
Toluene	2	890
Dimethyl formamide	2	880

TABLE 5: STATIC HEAD SPACE SAMPLING: A VIGABATRIN DRUG SUBSTANCE SAMPLE SPIKED WITH POSSIBLE RESIDUAL SOLVENTS, USING 1-PROPANOL AND 1,2-DI-CHLOROETHANE AS(INTERNAL STANDARD)[17].

Solvents	ICH Q3C class	ppm limit according to ICH
Methanol	2	3000
Ethanol	3	-
Acetone	3	-
Isopropyl alcohol	3	-
Methylene chloride	3	600
1-propanol (internal standard)	3	-
1,2-dichloroethane	3	1870
(internal standard)	3	-
Butanol	3	-
Toluene	3	890

TABLE 6: DYNAMIC HEAD SPACE SAMPLING: A STANDARD STOCK SOLUTION OF NINE ALCOHOLS WERE PREPARED IN WATER USING ETHYL METHYL KETONE AS INTERNAL STANDARD[35,36].

Solvents	ICH Q3C class	ppm limit according to ICH
Methanol	2	3000
Ethanol	3	-
1- propanol	3	-
2- propanol	3	-
1- butanol	3	-
2-butanol	3	-
tert- butanol	3	-
1- pentanol	3	-
2- pentanol	3	-
Ethyl methyl ketone (internal standard)	3	-

TABLE 7: HEAD SPACE SOLID PHASE MICROEXTRACTION (SPME): USING POLYDIMETHYLSILOXANE/DIVINYLBENZENE AS SPME FIBER[48,49].

Solvents	ICH Q3C class	ppm limit according to ICH
Acetonitrile	2	410
Dichoromethane	2	600
Chloroform	2	60
Tricholoroethylene	2	80
1,2- Dichloroethane	2	1870
benzene	1	2
1-4 Dioxane	2	380
Pyridine	2	200
Cyclohexane	2	3880
Toluene	2	890

TABLE 8: SINGLE DROP MICRO EXTRACTION: SDME FOR THE ANALYSIS OF TEN CHLOROBENZENES IN WATER SAMPLES[50]. USING A TOLUENE SOLUTION OF 1,4-DIBROMOBENZENE AS AN INTERNAL SATNDARD.

Solvents	ICH Q3C class	ppm limit according to ICH
1,3- dichlorobenzene	----	----
1,4- dichlorobenzene	----	----
1,2- dichlorobenzene	2	1870
1,3,5- trichlorobenzene	----	----
1,2,4- trichlorobenzene	----	----
1,2,3- trichlorobenzene	----	----
1,2,4,5- tetrachlorobenzene	----	----
1,2,3,4- tetrachlorobenzene	----	----
Pentachlorobenzene	----	----
Hexachlorobenzene	----	----

Spectroscopic and spectrometric methods[9]:

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[9] 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[9-33]:

The most useful analytical method of choice for identification and quantification of OVIs is the gas chromatography. Gas chromatographic procedures for OVIs can be carried out either by direct injection method, head space analysis, solid phase microextration method and the new technique known as single drop microextraction (SDME).

Direct injection method[2]:

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 costs of direct injection have 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 components. These injection techniques can also be used for concentrated samples commonly analyzed 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 the 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.

Head space gas chromatography[34]:

Head space sampling technique can be categorized into two types dynamic head space[35,36] and static head space analysis[17]. In dynamic head space technique, a continuous flow of gas is swept over the surface of a sample matrix. Volatiles from sample matrices are conveyed into a trap where the volatile residual solvents are accumulated prior to analysis[37-47]. A thermal desorption cycle of the trap is initiated, and a carrier gas takes the analyte into a gas chromatograph for the analysis. In the 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 the gas phase are injected into the 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 partition into the vapors phase above the sample and reach equilibrium. As a result their concentration in the vapor 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 fields of forensic, clinical, food and aroma analysis. This technique is robust, convenient and readily automated and validated and 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 drug 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 the equilibrium between the gas and sample. The head space techniques 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 analysis has the advantages of ease of use and automation. Disadvantages 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 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.

Solid phase micro extraction (SPME):

It involves extraction of specific organic analyte directly from the 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 solvent in pharmaceutical preparations[48-49]. 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[42] 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)[50]:

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. 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 a 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 extracting solvents that have been used for liquid-liquid SDME are hexane, n-octane, iso-octane, cyclohexane, n-hexadecane,

toluene, chloroform, butyl acetate, di-isopropyl ether. For head space SDME, the solvents are n-octane, n-decane, tetradecane, n-hexadecane, toluene, 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. Advantages of head space SDME are, high selectivity provided by wide range of extracting solvents, good quantitation and low detection limits. Fresh solvent for each sample eliminates sample carry over. Liquid extractant operates by absorption, resulting in high upper limits 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[51] was carried out by three methods, I, II and III. Later three additional methods were included which are methods IV, V and VI. In method I, the sample is analysed by direct aqueous injection technique with FID detector using G-27 column (5% phenyl and 95% methylpolysiloxane, 30 m×0.53 mm). In method II, the sample is analysed by dynamic head space technique with FID detector using G-25 (1% polyethylene glycol) packed column. In method III, the sample is analysed by dynamic head space technique with mass selective detector using G-25 (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) 30×0.53 mm. In method V, the sample is analysed by direct aqueous head space technique with FID using G-43 column (6% cyanopropylphenyl and 94% dimethyl polysiloxane) 30×0.53 mm.

In European Pharmacopoeia[34], three diluents, viz., water, N,N-dimethylformamide (DMF) and 1,3-dimethyl-2-imidazolidinone (DMI) are used for sample preparation. Two chromatographic systems are prescribed, but system A is preferred while system B is used normally for confirmation or identity. System A uses a fused capillary or wide bore column of 30×0.32 or 0.53 mm i.d. (6% polycyanopropylphenylsiloxane and 94% polydimethylsiloxane) with FID or ECD detector, using static head space technique with temperature programming. System B uses a fused capillary or wide bore column of 30×0.32 or 0.53 mm i.d., coated with macrogol 20000R film of thickness 0.25 mm with FID or ECD, 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 headspace sampling, a new technology known as Stop-Flow GC has been reported[52]. A stop-flow GC technique[53], 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 trifluoropropyl stationary phase. The separation was accomplished in 12 min. Resolution between coeluting or closely eluting components was substantially improved by introducing nine stop-flow pulses to tune the chromatographic separation.

Teledyne Tekmar 7000HT headspace autosampler unit in conjunction with stop-flow GC technology has been used for separation of class 1 and class 2 residual solvents. In stop-flow GC, the solvents were separated by passing the sample through a two- column ensemble consisting of a Stabilwax column and an Rtx-200 column 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.

CONCLUSIONS

Residual solvents from the processes in the manufacturing of pharmaceuticals are hazardous and cause serious problems and must be removed. Certain methods like thermogravimetric analysis, loss on drying are simple but lack specificity to identify the volatile analyte, spectroscopic and spectrometric methods lacked sensitivity. Gas chromatographic techniques are ideal for residual solvent analysis. They are selective for characterization of residual solvents and also sensitive to accurately determine these solvents in trace amounts, when present in pharmaceutical substances. Recognizing the need

to control the presence of these solvents, which are likely to cause undesirable toxic effects. United States Pharmacopoeia (USP-NF XXIV) has identified their potential hazardous effects and provides methods for their detection in pharmaceuticals. The methods includes direct injection method, head space analysis, solid phase microextration (SPME) method and the new technique known as single drop microextraction (SDME).

REFERENCES

1. International Conference on Harmonization, Impurities in new drug substances, 2002. Available from: http://www.ich.org.
2. Hymer CB. Residual solvent testing: A review of gas chromatographic and alternative techniques. Pharm Res 2003;23:337-44.
3. International Conference of Harmonization, Impurities in new drug substances, 1997. Available from: http://www.ich.org.
4. Haky JE, Stickney TM. Automated gas chromatographic method for the determination of residual solvents in bulk pharmaceuticals. J Chromatogr A 1985;321:137-44.
5. Organic volatile impurities. Pharm Forum 1988;14:3601-702.
6. United States Pharmacopeia, (USP-NF XXIV). Pharmacopoeial Convention Inc.: Rockville, Maryland, United States; 1995. p. 1877.
7. Karen MA, Handbook of Modern Pharmaceutical Analysis. Vol. III, Separations Science Technology, Academic Press: 2001. p. 86-95.
8. Camarasu CC. Head space SPME method development for the analysis of volatile polar residual solvents by GC-MS. J Pharm Biomed Anal 2000;23:197-210.
9. Osawa Z, Aiba M. Effect of residual solvent on photo degradation of Poly (vinyl chloride). Ploy Photochem 1982;2:339-48.
10. Li Z, Yieng HH, Gregory PM. Static headspace gas chromatographic analysis of the residual solvents in gel extrusion module tablet formulations. J Pharm Biomed Anal 2002;28:673-82.
11. Raquel O, Guillem C, Joan FD, José LF, Juan C. Static headspace gas chromatographic method for quantitative determination of residual solvents in pharmaceutical drug substances according to European Pharmacopoeia requirements. J Chrom A 2004;1057:193-201.
12. Raghani AR. High-speed gas chromatographic analysis of solvents in pharmaceuticals using solid phase microextraction. J Pharm Biomed Anal 2002;29:507-18.
13. Marie JR, Melanie, Julie B. Measuring residual solvents in pharmaceutical samples using fast gas chromatography techniques. J Chromatogr B 2004;805:77-86.
14. Weiyong Li. Trace analysis of residual methyl methanesulfonate, ethyl methanesulfonate and isopropyl methanesulfonate in pharmaceuticals by capillary gas chromatography with flame ionization detection. J Chrom A 2004;1046:297-301.
15. Legrand S, Dugay J, Vail J. Use of solid-phase microextraction coupled with gas chromatography for the determination of residual solvents in pharmaceuticals in pharmaceutical products. J Chrom A 2003;999:195-201.
16. Saprykin YA, Golovko B, Pazderski YA. Gas chromatographic analysis of volatile chlorides for organic and organochlorine impurities using a high-frequency emission detector. J Chrom A 2004;246:51-6.
17. Hercegova A, Domotorova M, Matisova E, Kirchner M, Otrekal R, Steluca V. Fast gas chromatography with solid phase extraction clean-up for ultratrace analysis of pesticide residues in baby food. J Chrom A 2005;1084:46-53.
18. Haky JE, Stickney TM. Automated gas chromatographic method for the determination of residual solvents in bulk pharmaceuticals. J Chromatogr A 1985;321:137-44.
19. Foust DW, Bergren MS. Analysis of solvent residues in pharmaceutical bulk drugs by wall-coated open tubular gas chromatography. J Chrom A 1989;469:161-73.
20. Chen TK, Moeckel W and Superhant HL. Modifications to the European Pharmacopeias proposal on residual solvents. Pharmeuropa 1992;4:62-7.
21. Rastogi SC. Gas chromatographic analysis of organic solvents mixtures on capillary columns of different polarity. Chromatographia 1993;37:211-4.
22. Deborah RW, Shila AH. Determination of impurities in "Yellow" Forase Pharm Sci 1984;73:115.
23. Kevin JM, Thomas WB. Analysis of organic volatile impurities as a forensic tool for the examination of bulk pharmaceuticals. J Chromatogr Biomed Appl 1996;686:85-95.
24. Clayton B, Hymer. Static headspace gas chromatographic method for the determination of residual solvents in vigabatrin drug substance. J Chrom A 1988;438:103-7.
25. Hong L, Attorfer H. A micro-sized technique for determination of organic volatile impurities in water-insoluble pharmaceuticals. Chromatograpia 2001;53:76-80.
26. Dennis KJ, Josephs PA. Proposed automated headspace method for organic volatile impurities (467) and other residual solvents. Pharm Forum 1992;18:2964-72.
27. Naughton VJ. A Micro-sized headspace GC technique for determination of organic volatile impurities in water - insoluble pharmaceuticals. Pharm Forum 1994;39:645.
28. Muligan KJ, McCauley H. Factors that influence the determination of residual solvents in pharmaceuticals by automated static headspace sampling coupled to capillary GC-MS. J Chromatogr Sci 1995;33:49.
29. Witschi C, Dweller E. Residual solvents in pharmaceuticals products: Acceptable limits influences of physicochemical properties, analytical methods and documented values. Eur J Pharm Biopharm 1997;43:215-42.
30. Narendra Kumar, John C, Egoville. Headspace gas chromatography method for the analysis of volatile impurities in a hormone replacement transdermal patch. J Chrom A 1999;859:113-8.
31. Willard HH, Merritt L, Instrumental methods of analysis. 7th ed. New Delhi; CBS Publishers and Distributors: 1986. p. 540.
32. Leonard CB. Remington the sciences and Practice of Pharmacy. Vol-1, Easton, PA; MAC Publishing Company: 1995. 52, p. 542.
33. Costin C, Camarasu. Head space SPME method development for the analysis of volatile polar residual solvents by GC-MS. J Pharm Biomed Anal 2000;23:197-210.
34. European pharmacopoeia, Directorate for the quality of medicines of the council of Europe, 4th ed. Strasboug, France; 2002.
35. Marinicher AN, Vilenberg AG, Bureiok AS. Efficiency of gas extraction in headspace analysis. J Chrom A 1992;600:251-6.
36. United States Pharmacopeia (USP-NF XXIV). Harmacopoeial Convention Inc.: Rockville, Maryland, United States; 1995. p. 1877.
37. Zhang Z, Pawliszyn J. Sampling volatile organic compounds using a modified solid phase microextraction device. J High Resol Chromatogr 1996;19:155-60.
38. Shirey R. Unknown residual solvents identification in drug products by headspace solid phase microextraction gas chromatography-mass spectrometry. J High Resol Chromatogr 1995;18:495-9.
39. Martos PA, Pawliszyn J. Calibration of soidphase microextration for air analysis based on physical chemical properties of the coating. Anal Chem 1997;69:206-15.
40. Pan L, Pawdeszyn J. Derivatization- solid phase microextraction: A new approach. Anal Chem 1997;69:196-203.
41. Gorecki T, Pawliszyn J. Solid phase microextraction /isothermal GC for rapid analysis of complex organic samples. J High Resol Chromatogr 1995;18:161-6.
42. Morcillo Y, Cai Y, Bayona JM. Rapid determination of methylene compounds in aqueous samples using solid phase microextraction and

capillary gas chromatography following in-situ derivation with sodium tetraethylborate. J High Resol Chromatogr 1995;18:776.
43. Grote C, Pawliszyn. Unknown residual solvents identification in drug products by headspace solid phase microextraction gas chromatography-mass spectrometry. J Anal Chem 1997;69:587-98.
44. Moens L, Smaelel TD, Dams R, Broede PV, Sandra P. Sensitive, Simultaneous determination of organomercury, lead, and tin compounds with solid phase microextraction capillary gas chromatography combined with inductively coupled plasma mass spectrometry. Anal Chem 1997;69:1604-11.
45. Lkso H, Ng WF. Determination of chemical warfare agents in natural water samples by soild-phase microextraction. Anal Chem 1997;69:1866-72.
46. Fromberg A, Nilsson T, Larsen BR, Montanarella L, Facchetti S, Madsen JO. Analysis of chloro and nitroanilines and benzenes in soils by headspace solid-phase microextraction. J Chromatogr 1996;746:71-81.
47. Page B, Lacroix G. Unknown residual solvents identification in drug products by headspace solid phase microextraction gas chromatography-mass spectrometry. J Cromatogr 1993;648:199-211.
48. Camarasu C, Mezel M, Szobo A. Headspace solid phase micro-extraction method optimization for residual solvent analysis. Acta Pharm Hung 1999;69:77-84.
49. Camarasu CC, Mezel SM, Varga GB. Residual solvents in pharmaceutical products by GC-HS and GC-MS-SPME. J Pharm Biomed Anal 1998;18:623-38.
50. Koji U, Atsuya H, Kazuichi U, Masayuki G. Matrix media selection for the determination of residual solvents in pharmaceuticals by static headspace gas chromatography. J Chrom A 2004;1057:203-10.
51. Derrick CW, James MM, Ingo C. Headspace liquid microextraction. LCGC North Am 2004;22:516-22.
52. Wallace B, Kancler J. One universal method for residual solvents in pharmaceuticals using a high temperature static headspace sample introduction. System application note 7000-021b.doc, Teledyne Tekmar Instruments: Feb 2004.
53. Wittrig RE, Dorman FL, English CM, Sachs RD. High speed analysis of residual solvents by flow-modulation gas chromatography. J Chrom A 2004;1027:75-82.

Accepted 10 May 2007
Revised 13 March 2007
Received 17 March 2006
Indian J. Pharm. Sci., 2007, 69 (3): 352-359