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Gas Chromatographic Method for Estimation of Organic Volatile Impurities in Some Ayurvedic Preparation

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Impurities in pharmaceuticals are undesired chemicals that are remaining with the active pharmaceutical ingredients (APIs) or developed during formulation, or upon aging of both API and formulated APIs to medicine. The presence of these undesired chemicals even in small amount may influence the efficacy and safety of the pharmaceutical products. The control of pharmaceutical impurity is a critical issue. Residual solvents in pharmaceuticals (commonly know as organic volatile impurities or OVIs) are organic volatile chemicals that are either used or produced during the manufacturing of active pharmaceutical ingredients, excipients and drug products and may be hazardous to human health. Residual solvents have no therapeutic benefits but may be hazardous to human health and to the environment, they are either not present in the products or are present only below acceptable levels. However, their acceptances limit and classification vary among the three major pharmacopoeias, USP, PhEur and JP. In the development and manufacture of chemical and pharmaceuticals, analytical chemistry plays a vital role in the quality control of the intermediate and final products. Separation methods occupy an important place in the array of available analytical techniques, depending on the nature of the compounds, gas chromatography methods continue to be used to a large extent, especially in automated routine controls. The use of specialized injection and detection methods has further increased its field of applications.

Key Words: Validation, Ayurvedic preparation, ICH, GC, Organic volatile impurities.

INTRODUCTION

The synthesis of an active pharmaceutical ingredient (API) normally consists of several synthetic steps. Process-related impurities can be formed at any step and could ultimately appear in the final drug substance, particularly in the scale-up drug candidates. Impurities must be controlled because of their potential toxicity. Impurity control is a continuing concern of regulatory agencies and the pharmaceutical industry. The International Conference on Harmonization (ICH) was formed

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in the 1990s to coordinate the technical requirement for the registration of pharmaceuticals in the European Union, Japan and the United States. ICH has issued the guideline Impurities in New Drug Substances, recommending that, for a maximum daily dose of less than or equal to 2 g per day, any impurity at the 0.10 % level (or 1 mg per day intake, whichever is lower) must be identified. The food and drug administration (FDA) has adopted the ICH guidelines and has published the guidelines in the federal register. The term tolerable daily intake (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term acceptable daily intake (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term permitted daily exposure (PDE) is defined in the guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance[1]. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class I: Solvents to be avoided
Class II: Solvents to be limited
Class III: Solvents with low toxic potential

Residual solvents are solvents that are used during the manufacturing process and may be detected after the product is in its final form[2]. Some of the common solvents are benzene, ethanol, toluene,chloroform, 1,4-dioxane, methylene chloride and trichloroethylene. Residual solvent in the active ingredient or drug product can come from many different stages in the manufacturing process (active substance granulation, milling, or drug product coating). Because the toxicity of most solvents has been well investigated, it is fairly easy to select appropriate control for residual solvents that may be found in the final dosage form. The most common technique for measuring residual solvents is gas chromatography because of the small size and volatile nature of solvent molecule.

EXPERIMENTAL

Chromatographic system-consisted of ESHIKA MICROPROCESSOR, gas chromatography.

Water (HPLC grade), methanol (HPLC grade), ethanol (AR grade), isopropyl alcohol (HPLC grade), methylene chloride (GR grade), chloroform (AR grade), 1,4-dioxane (AR grade). All the glassware used were of A1 grade. All the solvents and chemicals used work were either AR or HPLC grade. Whatman filter paper No. 41 used through out the experiment.

Chromatographic condition: In the proposed method, the following working instrumental variables were enabling on gas chromatography. The column temperature was maintained at 70 ºC, the injection port temperature was 150 ºC and detector temperature 150 ºC The flow rate of carrier gas was 10mL/min with control mode of split of ratio 1:2. The column pressure was initially maintained at 30 kpa.

Validation approach: All working solution were made with HPLC grade water to get concentration of methylene chloride (500 ppm), ethanol (500 ppm), isopropyl alcohol (500 ppm). Chloroform (50 ppm), 1,4-dioxane(100 ppm) standard organic volatile impurities was prepared in combination. One µL of this was analyzed by gas chromatography. The analysis was repeated 7 times. Result was then recorded on data sheet (Table-1). The method was validated for accuracy, precision, specificity, detection limit, quantification limit and robustness. The internal standard used was methanol.

TABLE-1
LINEARITY RESULT OF ETHANOL

Data No.	%	Conc. (ppm)	Ratio of analyte / IS		Mean	Variation (%)
–	0	0	0		0	0
14	60	300	I	0.8231	0.8238	0.08
15			II	0.8246		
16	80	400	I	1.1066	1.0986	0.8
17			II	1.0907		
08	100	500	I	1.3718	1.3707	0.1
09			II	1.3697		
18	120	600	I	1.6517	1.6538	0.2
19			II	1.6560		

Equation: $y = 0.0027x$; $n = 5$; $R^2 = 1$.

The repeatability % RSD was found to be less than 2 % and SD (+) less than 1 %. The linearity was found to be in the range (0-600) (Fig. 1).

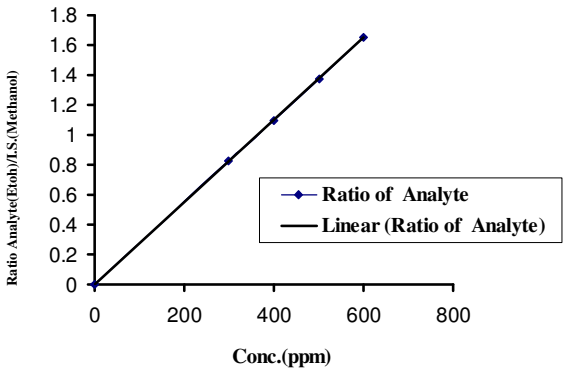

Fig. 1. Linearity result of ethanol, internal standard analysis, curve type: linear $y = 0.0027x$, Origin: Include, Corelation coefficient (R^2) = 1

Linearity of ethanol was calculated using internal standard method. The internal standard was results are mean of 2 replicate, methanol (500 ppm).

Repeatability of organic volatile impurities was calculated using internal standard method[2] (Table-2). The internal standard was methanol (500 ppm).

TABLE-2
REPEATABILITY STUDIES OF STANDARD ORGANIC VOLATILE IMPURITIES

Data No.	Standard run	Ratio of analyte peak area to that of internal standard				
		Ethanol	Isopropyl alcohol	Methylene chloride	Chloroform	1,4-Dioxane
		500 ppm	500 ppm	500 ppm	50 ppm	100 ppm
07	Replicate 1	1.3812	1.4603	0.7704	0.0483	0.2718
08	Replicate 2	1.3718	1.4531	0.7655	0.0482	0.2720
09	Replicate 3	1.3697	1.4493	0.7558	0.0483	0.2719
10	Replicate 4	1.3788	1.4553	0.7647	0.0488	0.2710
11	Replicate 5	1.3779	1.4602	0.7688	0.0484	0.2725
12	Replicate 6	1.3808	1.4615	0.7747	0.0485	0.2740
13	Replicate 7	1.3703	1.4463	0.7693	0.0486	0.2729
	Mean	1.3757	1.4551	0.7670	0.0484	0.2723
	± SD	0.0050	0.0059	0.0059	0.0002	0.0009
	% RSD	0.3634	0.4054	0.7692	0.4132	0.3305

The validated system was applied for estimation of organic volatile impurities[3] in certain popular ayurvedic film coated marketed formula.

Distillation of marketed preparation: (IP method III C modified): An accurately weighed 10 g of film coated tablets marketed formulation (Table-3) crushed to fine powder was mixed thoroughly. It was then transferred to the distillation flask along with 150 mL of HPLC grade water. To it little pumice powder was added and attached to the distillation head. It was then heated up to 100 ºC and about 100 mL of distillate was collected. One µL of this was injected and chromatograms were obtained. 500 ppm of internal standard (methanol) was added to the distillate collected. One µL of this was injected and chromatograms were again obtained. The analysis are given in Tables 4 and 5.

TABLE-3

Name of preparation	Batch No.	Mfg. Date	Sample code
Livfit tablet	3038	Apr. 03	L -1
	4FJ040	Sep. 04	L -2
	4FJ026	July. 03	L –3
Rumastal tablet	115	Aug. 02	R-1
	118	Mar. 04	R-2
	ANO4002	July. 04	R-3

RESULTS AND DISCUSSION

The system was validated for each of the solvent as per the guidelines of the ICH. The values are presented below.

Under the optimized condition, linearity range, repeatability, limit of detection and quantization and acceptable limit of the analyte were determined. The result are shown in the Table-6.

TABLE-4
GAS CHROMATOGRAPHIC ANALYSIS OF LIVFIT TABLET (SOLID DOSAGE FORM)

Sample	Amount taken (g)	According to USP/EP limit of OVI in ppm					Detected OVI in ppm					
		EtOH	IPA	M. chloride	Chloroform	1,4-Dioxane	MtOH	EtOH	IPA	M. chloride	Chloroform	1,4-Dioxane
L-1	10.04	500	500	500	50	100	–	–	–	–	–	–
L-2	10.03	500	500	500	50	100	–	–	–	–	–	–
L-3	10.06	500	500	500	50	100	5.90	–	–	–	–	–
					Mean		–	–	–	–	–	–
					± SD		–	–	–	–	–	–
					% RSD		–	–	–	–	–	–

TABLE-5
GAS CHROMATOGRAPHIC ANALYSIS OF
RUMASTAL TABLET (SOLID DOSAGE FORM)

Sample	Amount taken (g)	According to USP/EP limit of OVI in ppm					Detected OVI in ppm				
		EtOH	IPA	M. chloride	Chloroform	1,4-Dioxane	EtOH	IPA	M. chloride	Chloroform	1,4-Dioxane
R-1	10.06	500	500	500	50	100	–	–	–	–	–
R-2	10.05	500	500	500	50	100	–	–	–	–	–
R-3	10.07	500	500	500	50	100	–	–	–	–	–
					Mean		–	–	–	–	–
					± SD		–	–	–	–	–
					% RSD		–	–	–	–	–

TABLE-6
VALIDATION PARAMETER

Compound	Linearity range (ppm)	r^2	Repeatability % RSD (n = 7)	LOD and LOQ (ppm)	Acceptable limits (ppm)
Ethanol	0-600	0.9999	0.3634	50	500
Isopropyl alcohol	0-600	1.0000	0.4054	50	500
Methylene chloride	0-600	1.0000	0.7692	50	500
Chloroform	0-60	0.9998	0.4132	10	50
1,4-Dioxane	0-120	0.9999	0.3305	5	100

The linearity was obtained in the range 0-600 ppm. Correlation coefficient (r^2) varied from 1 to 0.9998. Limit of detection and quantization in GC system for each organic volatile impurities ranges from 5 to 50 ppm and the acceptable limit according to USP/PhEur ranges from 50-500 ppm. The repeatability was determined by

performing seven replicate from the data obtain % RSD was found to be 0.4054 for most of the analyte, except for methylene chloride, which was found to be 0.7692. The result obtained in system suitability experiments indicates that: The system under the optimized condition ensures the results of acceptable quality.

The proposed validated GC system was extended for determination of organic volatile impurities in various films coated tablet marketed formulation for different batches.

It was generally found from the retention time of a peak in the chromatogram methanol, ethanol and isopropyl alcohols are present as organic volatile impurities.

• Quantification of this peaks led to establishing concentration level.

Livfit Tab (L-3): Methanol 5.90 ppm.

Rumastal Tab (R-1, R-2, R-3): No impurity was found.

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