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A Concise Study of Organic Volatile Impurities in Ten Different Marketed Formulations by [GC/HS-FID/MS] Gas Chromatography Technique

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Abstract

Organic solvents such as Methanol, Isopropyl alcohol and Dichloromethane frequently used in sustained release or controlled release dosage form in pharmaceutical industry for coating. The good choice of solvent for coating of modified release dosage form is Methanol, Isopropyl alcohol and Dichloromethane. A selective Gas Chromatographic GC/HS-FID method has been developed and validated as per ICH guidelines for residual solvent quantification and confirmed the mass number by GC/HS-MS method. The separation was carried out on DB 624 column (30 m, 0.53 mm, [ID] 0.25 mm coating thickness), using Perkin Elmer/Clarus 500 GC/MS, with nitrogen as carrier gas in the split mode by head space injection method. The method described is simple, sensitive, rugged, reliable and reproducible for the quantization of Isopropyl alcohol, methanol and Dichloromethane at residual level in marketed modified release dosage form. In this paper completely demonstrated the method of quantification of residual solvents by GC/HS/FID and confirming by GC/HS/MS of the residual solvents present in 10 different marketed products availed in southern part of India. The enteric coated product has been selected and experiment was performed.

Keywords: Enteric coated formulations; Gas chromatography; Head Space; Mass spectroscopy; Residual solvents

Introduction

Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used to produce in the manufacturer of drug substance or excipients or in the preparation of drug product. Residual solvent do not provide any therapeutic benefit that should be removed to the maximum possible level fulfilling quality based requirements as per ICH guideline this is one of the standards to control the quality and purity of the pharmaceutical substance, excipients and drug products [1,2]. During the manufacturing process, certain types of formulations like gel extrusion module tablet (GEM), extrusion and spheronization (ES) techniques and enteric or modified release tablets often using solvents like methanol, isopropyl alcohol and dichloromethane [3-5].

Most of the pharmaceutical modified release dosage form having different type organic solvents that differ in molecular weight, polarity and volatility. For complex samples like these, head space sampling is the fastest and cleanest method [6-8]. A head space sample is normally prepared in vial containing the sample, dilution solvent, matrix modifier and the head space. Volatile compounds from complex sample mixture can extract from non volatile sample components and isolated in head space or vapor portion of a sample vial [9,10].

Experimental Method

Instruments and materials

Gas Chromatograph Perkin Elmer Clarus 500 was used in the development and validation of GC method. Gas chromatograph was equipped with standard oven for temperature programming, split/split less injection ports and flame ionization detector. DB-624 column (30 m×0.53 mm [ID]×0.25 µm coating thickness, 6% cyanopropyl phenyl and 94% dimethyl polysiloxane stationary phase), with nitrogen as carrier gas in the split mode by head space injection method was used. Analytical grade solvents isopropyl alcohol, methanol and dichloromethane were used as standard and dimethyl sulphoxide (DMSO) were used as solvent and it was purchased from Thomas Baker, Mumbai, India. Ten different branded extended release coated formulations were purchased from chemist shop which is situated in the southern part of India.

Preparation of standard

Isopropyl alcohol, methanol and dichloromethane were prepared at the concentration of 1000 µg/mL, 300 µg/mL and 120 µg/mL respectively by diluting with DMSO. 5 mL of the above solution was transferred into head space vial and crimped properly and analyzed in GC system. The standard was analyzed by GC/HS/FID and the response was used for the calculation of amount of residual solvents from the FID detector. The standard was analyzed by GC/HS/MS for determined the standard mass number of the each residual solvent.

Preparation of sample

Accurately weighed and crushed ten units in each brand of tablets. 500 mg of crushed tablet powder transferred in to head space vial and added 5 mL of DMSO and crimped properly. The sample was analyzed by GC/HS/FID and the quantification was done by the response found from the FID detector. The sample was analyzed by GC/HS/MS for confirming the mass number of the each residual solvent.

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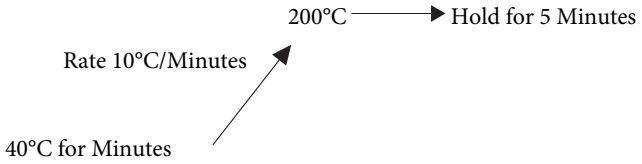
Temperature programming



Initially temperature was maintained 40°C for 4 minutes and raise to 200°C at the rate of 10°C then hold for 5 minutes.

Gas chromatographic conditions

Gas chromatographic conditions were shown in Table 1.

Head space parameter

Head Space Parameters were shown in Table 2.

Mass conditions

Mass conditions were shown in Table 3.

Method validation

The analytical method validation was carried out as per ICH method validation guidelines [2]. The validation parameters addressed were System suitability, Precision, Linearity, and Limit of detection [LOD], Limit of quantization [LOQ], Accuracy, Robustness and Ruggedness.

Carrier Gas	Nitrogen
Flow	1.5 mL/Minutes
Split ratio	1:30
Detector Temperature	250
Hydrogen/zero air	1:10
Attenuation	-3
Run Time	25 Minutes

Table 1: Gas chromatographic conditions.

Temperature		Timing	
Carrier	18 Psi	Pressurization	2 minutes
Needle	70°C	Inject	0.05 minutes
Transfer line	80°C	Withdraw	0.2 Minutes
Oven	60°C	Thermostat	15.0 Minutes
GC Cycle			25.0 minutes

Table 2: Head Space Parameter.

Scan Type	Full
Scan Range	27 to 170 m/z
Scan Time	2 s
Library	NIST-011

Table 3: Mass conditions.

System suitability

Six standard injections were injected and the percent related standard deviation was calculated.

Precision

Accurately weighed and crushed ten units each brand of tablets. 1 g of each brand of crushed powder mixed in a mortar. Then weighed 500 mg of mixed tablet powder transferred in to head space vial and spiked the standard at the target concentration and analyzed spiked and unspiked samples by GC/HC/FID, concentration of each solvent was calculated and the true concentration was obtained the subtracted value from the unspiked sample (Table 4).

Linearity

Linearity was established from the range of LOQ to 200% of the target concentration for each solvent. Linearity graph was plotted concentration of each solvent against response of the each solvent (Table 5).

LOD & LOQ establishment

LOD and LOQ was established by S/N ratio method, signal to noise ratio was found closer to 10 for limit of quantization and 3 for limit of detection (Table 6).

Accuracy

Accuracy was established LOQ to 200% of the target concentration, standard solution was spiked in the mixture of the crushed formulations.

Robustness and Ruggedness

Analytical parameters were deliberately changed and the system suitability was checked. Initial temperature of the gradient program and flow of the carrier gas was changed ± 2 number for chromatographic condition. Different brand of column was used. Head space parameter needle, oven and transfer line temperature was changed ± 10%. For intermediate precision experiment was performed with another analyst (Table 7).

Results and Discussion

Gas chromatographic method for the determination of residual solvents in marketed formulations by GC/HS/FID and the mass number of the respective residual solvent was confirmed by GC/HS/FID/MS. Residual solvent method was developed and validated as per ICH guidelines and the parameter was explained above. System suitability was performed and the percent related standard deviation and bracketing standard was found below 15.0% for the entire activity.

Sample	Isopropyl alcohol		Methanol		Dichloromethane	
	Area	Concentration µg/g	Area	Concentration µg/g	Area	Concentration µg/g
1	10321	5089	11542	3141	9051	583
2	10412	4667	12542	2891	8478	622
3	10235	4973	11412	3177	9245	570
4	10741	4863	10243	3539	8954	589
5	10254	4769	11541	3141	8124	649
6	10235	4985	12543	2890	8154	647
Average		4891	Average	3130	Average	610
SD		155.2	SD	238.6	SD	34.0
% RSD		3.2	% RSD	7.6	% RSD	5.6

Table 4: Precision.

S.No	Isopropyl alcohol		Methanol		Dichloromethane	
	% Level	Area	% Level	Area	% Level	Area
1	LOQ	53	LOQ	55	LOQ	74
2	2	165	5	621	13	1254
3	5	501	33	3901	17	1485
4	20	2514	50	6121	83	7543
5	30	3321	67	7695	125	8297
6	100	10542	100	11854	100	9051
7	120	13214	125	13214	125	11541
8	150	15210	167	16541	167	15847
9	170	17854	183	19237	183	16841
10	200	20145	200	23084	200	18012
[R^2]		**0.997**		**0.997**		**0.998**

Table 5: Linearity.

Solvents	Concentration (ppm)	Area	S/N ratio
Isopropyl alcohol	23	53	9.56
Methanol	25	55	10.42
Dichloromethane	11	81	10.31

Table 6: LOQ.

S.No	Name	Isopropyl alcohol		Methanol		Dichloromethane	
		Concentration (µg/g)	Mass Number	Concentration (µg/g)	Mass Number	Concentration (µg/g)	Mass Number
1	Brand # 1	500	45	221	32	140	84
2	Brand # 2	240	45	Not Detected		Not Detected	
3	Brand # 3	Not Detected		654	32	230	84
4	Brand # 4	212	45	Not Detected		Not Detected	
5	Brand # 5	843	45	215	32	Not Detected	
6	Brand # 6	214	45	241	32	Not Detected	
7	Brand # 7	Not Detected		850	32	214	84
8	Brand # 8	321	45	154	32	Not Detected	
9	Brand # 9	854	45	Not Detected		210	84
10	Brand # 10	541	45	798	32	Not Detected	

Table 7: Concentration of residual solvent in different brand.

Parameter	Acceptance criteria	Results
System Suitability	% RSD Not More Than 15.0%	1.6% to 8.1%
Precision	% RSD (six sample preparation) Not More Than 15.0%	@ LOQ level – 7.7 to 12.2% and 100% Level 3.2 to 7.6%
Linearity	Correlation coefficient Not Less Than 0.995	0.997 to 0.998
Accuracy	Percent Recovery 85.0% to 115.0%	90.0 to 107.0% [Overall recovery form LOQ to 150%]
Robustness and Ruggedness	% RSD Not More Than 15.0%	4.1 to 8.1% [Overall compilation of system suitability]

Table 8: Overall compilation of validation [Results of entire study].

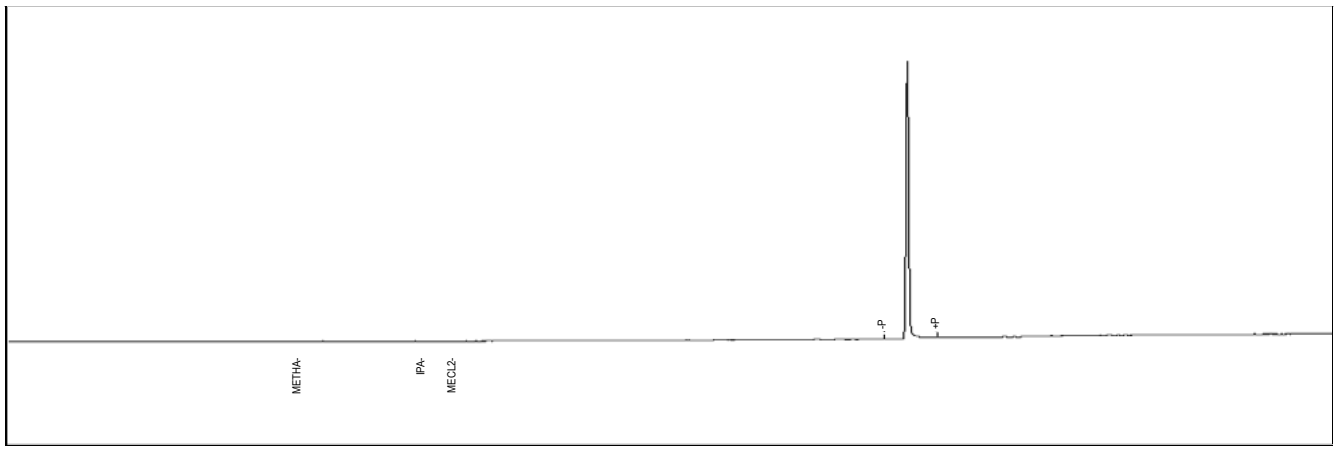


Figure 1: Typical chromatogram of Blank.

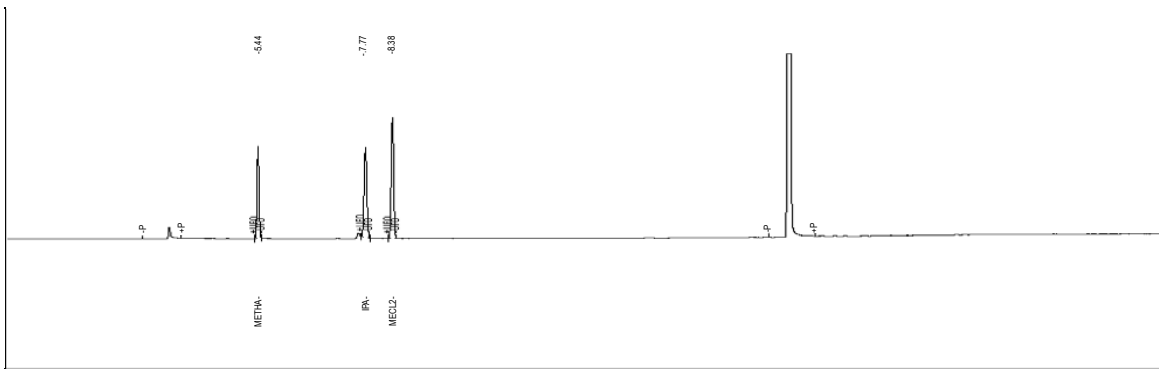


Figure 2: Typical chromatogram of Standard.

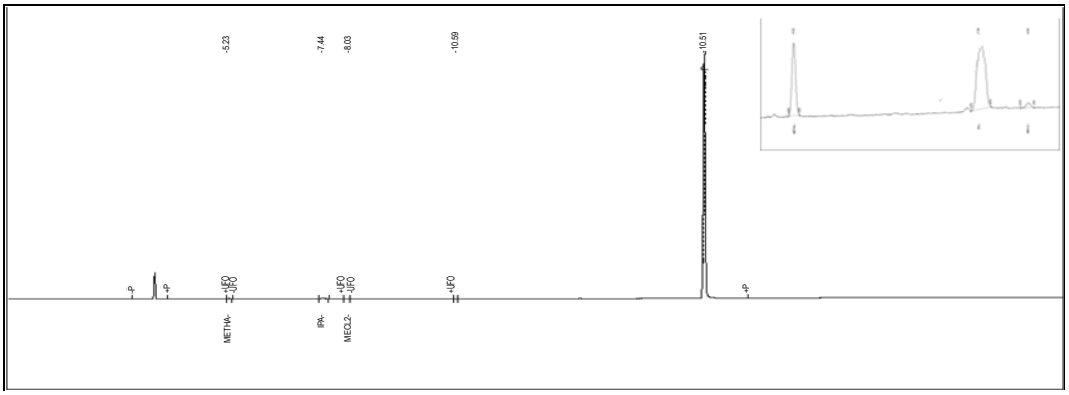


Figure 3: Typical chromatogram of Sample Brand 1.

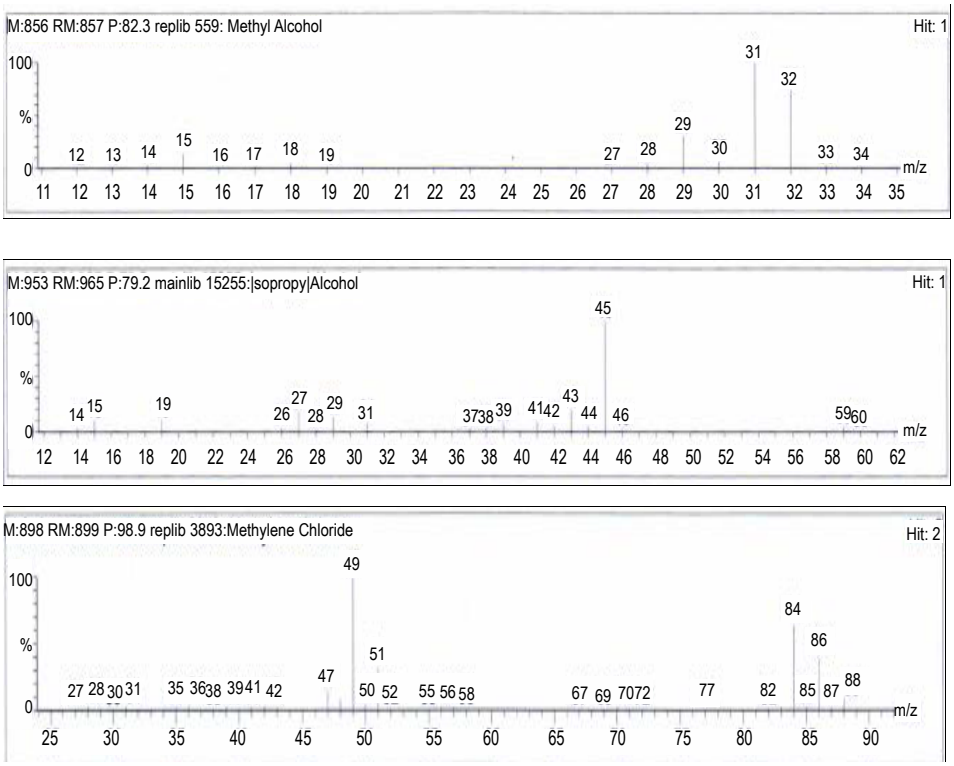


Figure 4: Typical Mass spectrum Sample#1.

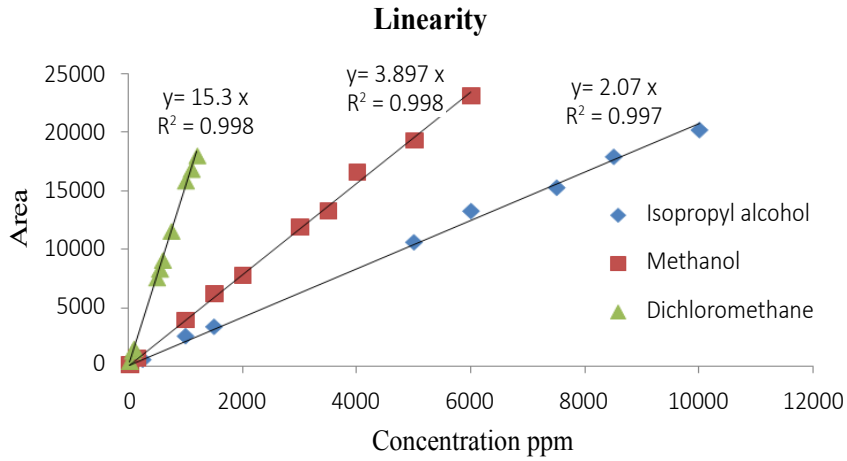


Figure 5: Linearity.

Precision was performed in spiked samples at targeted concentration and LOQ concentration for each solvents and the percent relative standard deviation of six sample preparations was found 3.2 to 7.6% for 100% level and 7.7% to 12.2% for LOQ level each solvent respectively. Linearity was established from LOQ to 200% of the target concentration and the correlation coefficient was found 0.997 to 0.998. Accuracy was performed from LOQ to 200% at five levels from the target concentration in mixed formulations powder, recovery was found 90.0% to 107.0% at each level each solvent. Range was covered from the precision, linearity and accuracy section. Robustness and Ruggedness was proven by the suitability of the method and the percent related standard deviation was found 4.1% to 8.1% for this activity. Each sample was analyzed by GC-HS/MS and mass number of the each solvent in each sample was compared with the standard mass number. Hence it is conforming the particular solvent may be methanol, isopropyl alcohol and dichloromethane and the detailed results tabulated in Table 8. Concentration of each solvent was with in the limit as per the ICH guidelines [Q3C (R5)]. Compiled validation result tabulated in Table 8. Typical chromatogram, mass spectrum and linearity plot refer Figures 1 to 5.

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