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A CONCISE STUDY OF ORGANIC VOLATILE IMPURITIES IN TEN DIFFERENT MARKETED FORMULATIONS BY [GC/MS] GAS CHROMATOGRAPHY / MASS TECHNIQUE

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Abstract

Aims

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.

Methods

A selective Gas Chromatographic Head Space flame ionization technique (GC/HS-FID) method has been developed and validated as per ICH guidelines (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) for residual solvent quantification and confirmed the mass number by GC/HS-MS method. The separation was carried out on DB 624 column (30m, 0.53mm, [ID] 0.25mm coating thickness), using Perkin Elmer/Clarus 500 GC/MS, with nitrogen as carrier gas in the split mode by head space injection method.

Results

System suitability was performed and the percent related standard deviation and bracketing standard was found below 15.0% for the entire activity. 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

Discussion

Determination of solvents used for coating purpose in pharmaceutical formulations was described in some article by GC/HS method and some article studied by GC/HS/MS method. In this study concentrated for marketed samples which are unknown solvent. The unknown solvent was identified and characterized by GC/MS.

Conclusion

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 and 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].

During the manufacturing process, certain types of formulations like Gel extrusion module tablet (GEM), Extrusion & Spheronization (ES) techniques and enteric or modified release tablets often using solvents like Methanol, isopropyl alcohol and Dichloromethane.

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. 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.

MATERIALS AND METHODS

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 (30m X 0.53mm [ID] X 0.25µm 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.

Isopropyl alcohol, Methanol and Dichloromethane was prepared at the concentration of 1000µg/mL, 300µg/mL and 120µg/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.

Accurately weighed and crushed ten units in each brand of tablets. 500mg of crushed tablet powder transferred in to head space vial and added 5mL 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.

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

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

Head Space Parameter

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

Mass conditions

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

Results

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.

System suitability was performed with six standard injections were injected and the percent related standard deviation was calculated.

Table 1: System Suitability

Injection	Area		
	Isopropyl alcohol	Methanol	Dichloromethane
1	10542	11651	8485
2	10021	10254	8754
3	10651	12541	8651
4	10254	11524	8854
5	10541	11254	8832
6	10614	11524	8714
Average	10437	11458	8715
Standard Deviation	247	736.2	135.3
% RSD	2.4	6.4	1.6

Precision was performed accurately weighed and crushed ten units each brand of tablets. 1g of each brand of crushed powder mixed in a mortar. Then weighed 500mg 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 2: Precision

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 3: Precision @ LOQ Level

Sample	Isopropyl alcohol	Methanol	Dichloromethane
1	50	55	74
2	49	50	65
3	55	68	81
4	52	51	70
5	63	52	71
6	60	53	68
Average	54.8	54.8	71.5
SD	5.6	6.7	5.5
% RSD	10.3	12.2	7.7

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 4: Linearity

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**	

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.

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

Table 5: LOQ

Solvents	Concentration (ppm)	Area	S/N ratio
Isopropyl alcohol	23	53	9.56
Methanol	25	55	10.42
Dichloromethane	5	74	10.12

Robustness and Ruggedness of the 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 6: Robustness

Temperature Variation

Parameter	Isopropyl alcohol			Methanol			Dichloromethane		
	38°C	40°C	42°C	38°C	40°C	42°C	38°C	40°C	42°C
Average area	13542	12542	10754	13241	11851	9840	9521	8714	7514
Average RT	8.2	7.8	6.5	6.8	5.2	3.8	9.7	8.4	7.2
% RSD	6.1	6.1	5.1	4.1	8.1	4.3	5.2	3.2	6.1

Flow Variation (mL per minutes)

Parameter	Isopropyl alcohol			Methanol			Dichloromethane		
	1.3	1.5	1.7	1.3	1.5	1.7	1.3	1.5	1.7
Average area	12142	12542	12154	11241	11851	11524	8821	8714	8514
Average RT	8.2	7.8	7.1	5.4	5.2	4.9	8.7	8.4	8.0
% RSD	4.1	6.1	4.1	4.1	8.1	7.3	2.2	3.2	7.1

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. 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 7. 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 Figure 1 to Figure 8.

Table 7: Concentration of residual solvent in different brand

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

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 & Ruggedness	% RSD Not More Than 15.0%	4.1 to 8.1% [Overall compilation of system suitability]

Fig 1: Typical chromatogram of Blank

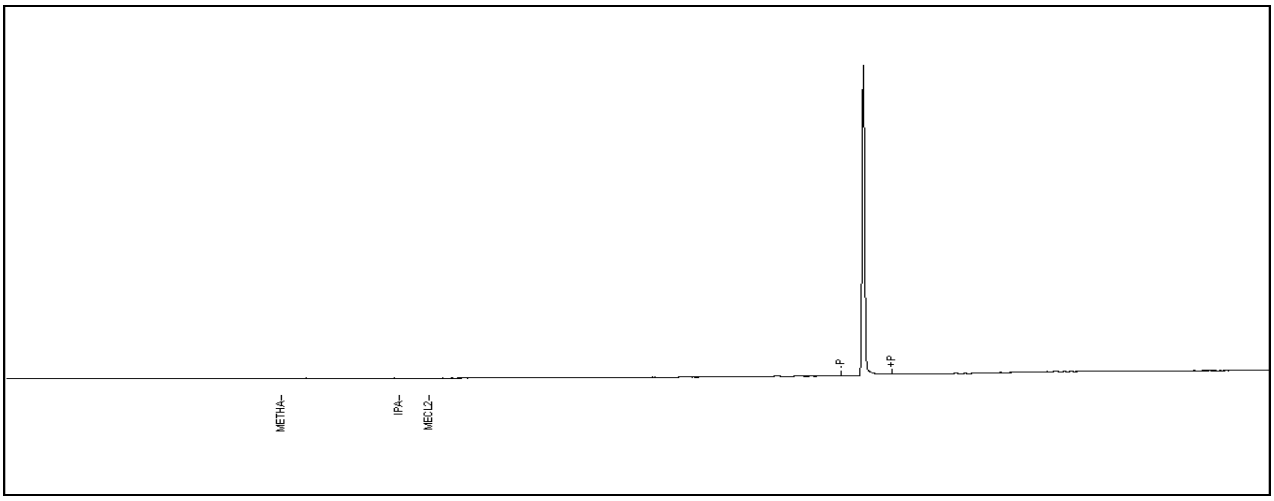


Fig 2: Typical chromatogram of Standard

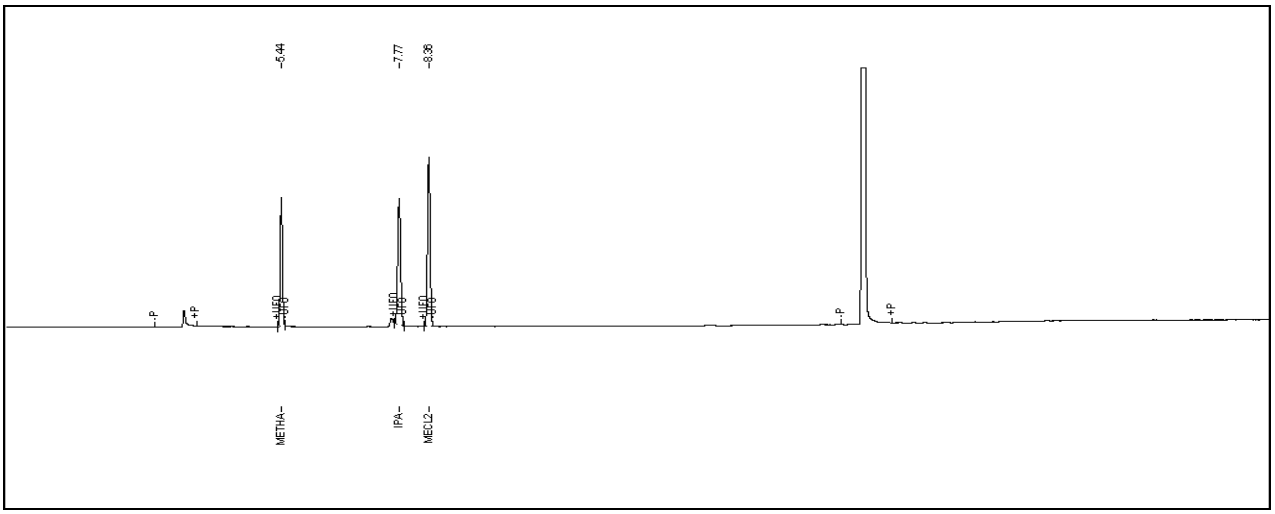


Fig 3: Typical chromatogram of Sample Brand 1

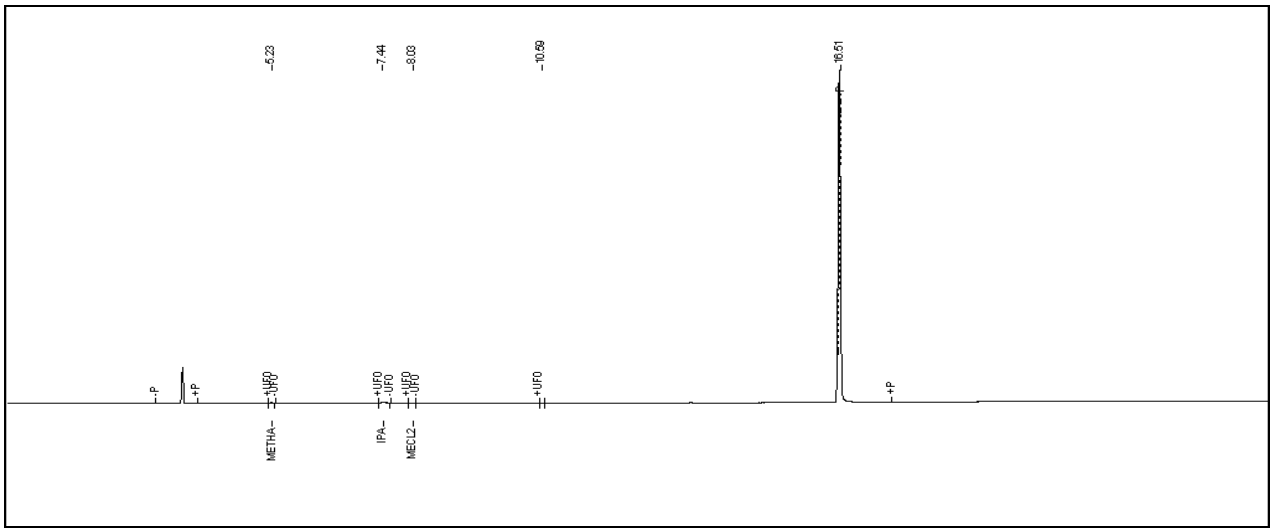


Fig 4: Typical chromatogram of Sample Brand 2

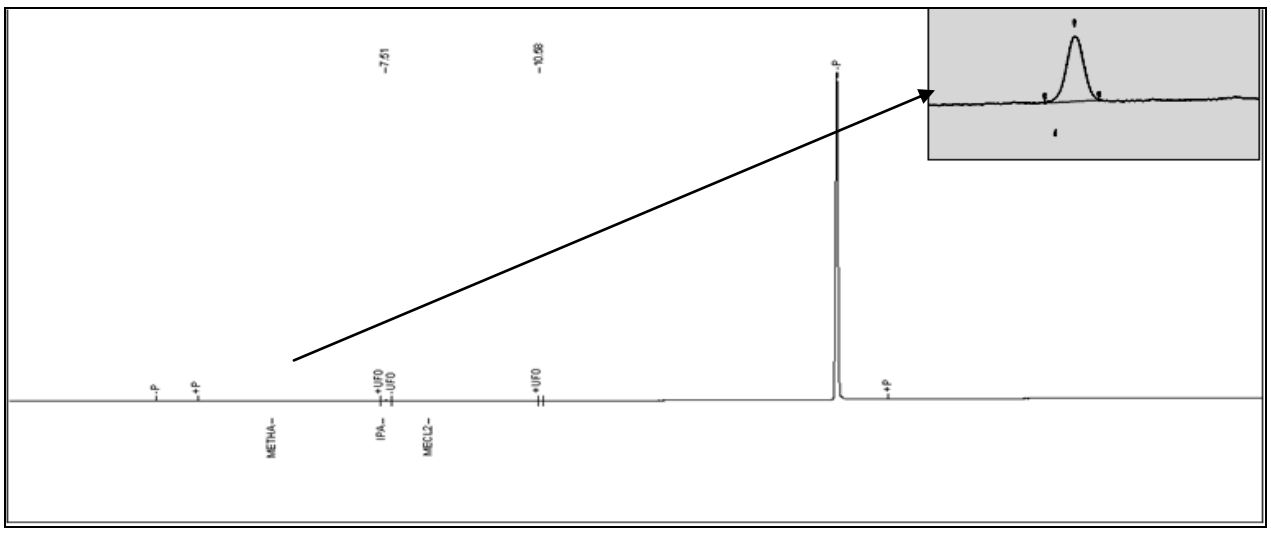


Fig 5: Typical chromatogram in GC/MS

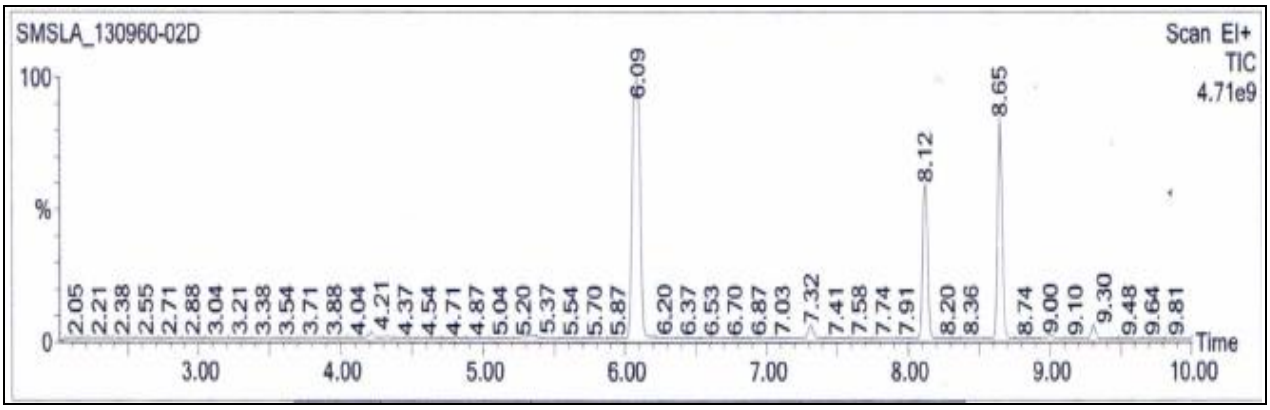
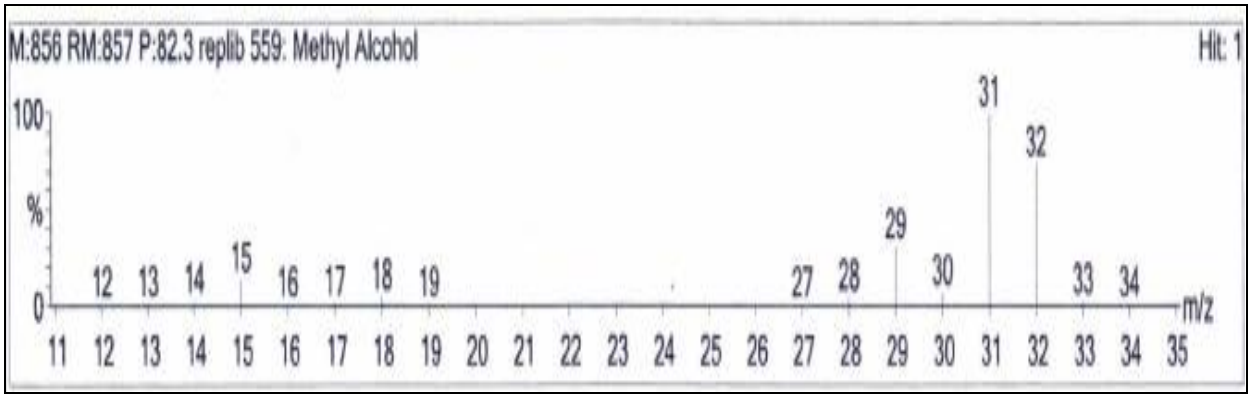
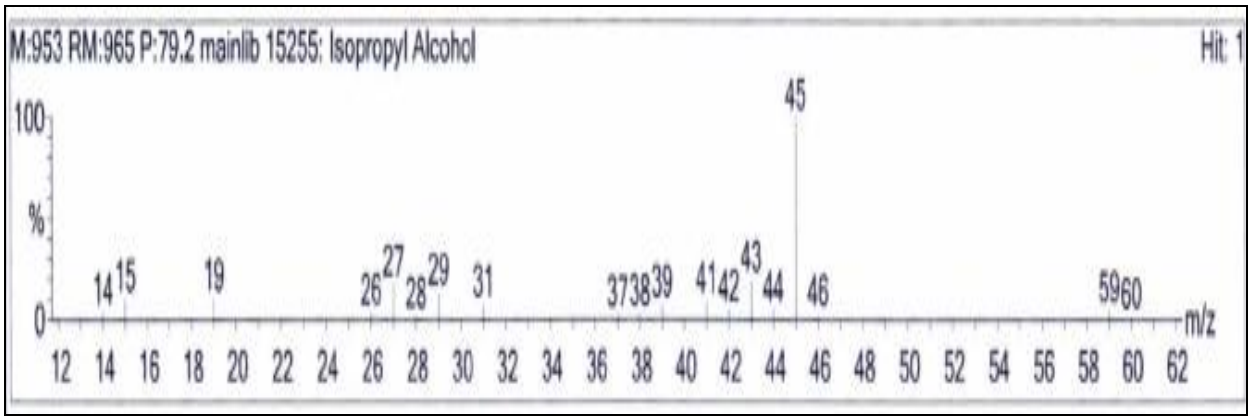


Fig 6: Typical Mass spectrum Sample#1





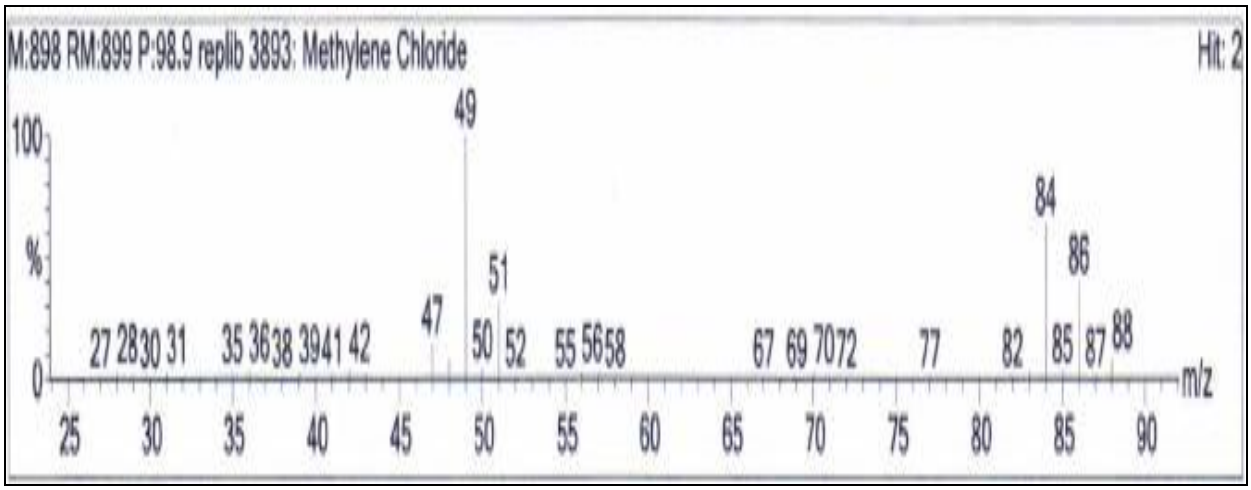


Fig 7: Typical Mass spectrum Sample#2

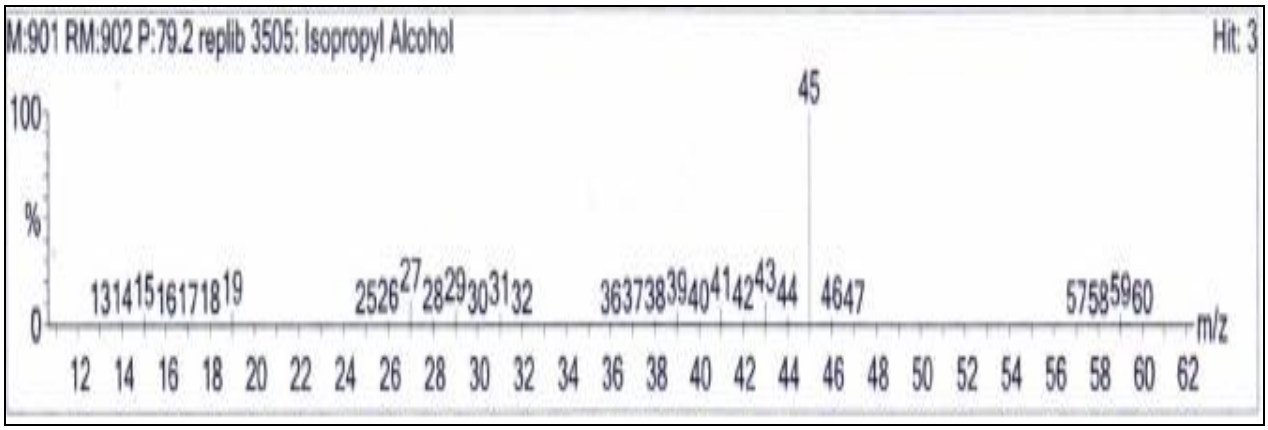
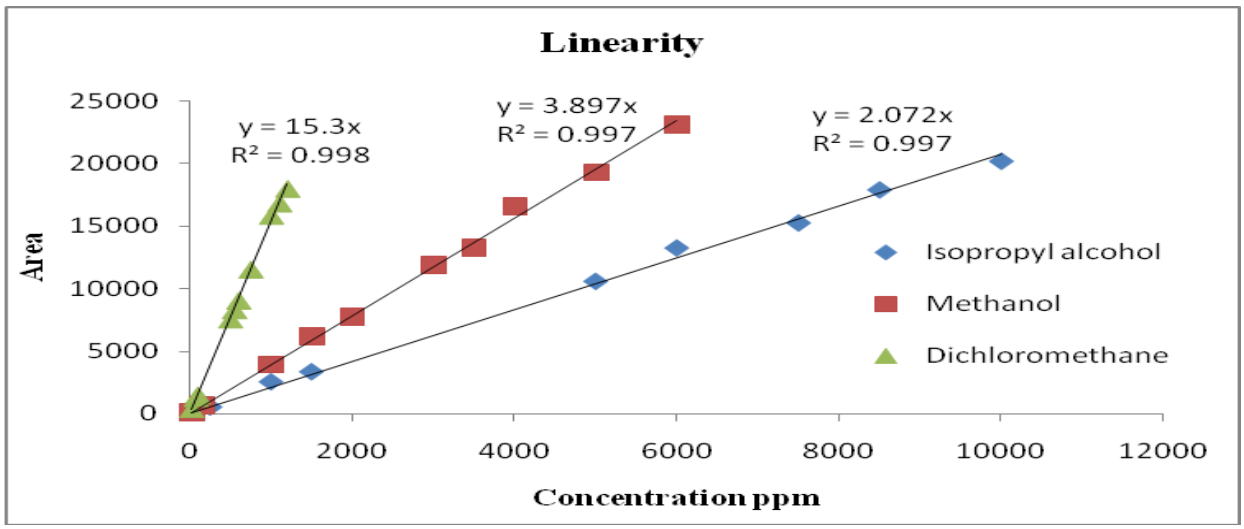


Fig 8: Linearity



Conclusion

This study presents a simple and validated GC/HS/MS method for estimation of residual solvents in marketed enteric coated formulations. The method developed is specific, accurate, precise and rugged. The content of organic volatile impurities present in the marketed enteric coated formulations was found to be within the ICH limits.

Conflict of Interest

The authors do not have any conflict of interest.

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