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Simultaneous Estimation of Residual Solvents (Isopropyl Alcohol and Dichloromethane) in Dosage Form by GC-HS-FID

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A simple and sensitive method for the determination of isopropyl alcohol and dichloromethane as residual solvent was developed and validated on gas liquid chromatography with headspace sampler fitted with flame ionization detector (GC-HS-FID). The carrier gas was helium and separation was carried out on Elite-624 (30 meter, 0.53 mm ID, 3µm df) capillary column consisting of 6 % cyanopropylphenyl - 94 % dimethyl polysiloxane stationary phase. The retention time for isopropyl alcohol and dichloromethane were 10.8, 11.4 min, respectively.

Key Words: Isopropyl alcohol, Dichloromethane, GC-HS-FID.

INTRODUCTION

For pharmacopeial purpose, residual solvent in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Organic solvents are entrapped within the formulation either during the course of manufacture of active pharmaceutical ingredients or during the coating of the formulation. These solvents are used frequently to dissolve film-coating materials to facilitate application onto compressed tablets[1,2].

These tablets are subjected to air-drying to remove all the organic solvents from the coat of finished product. The residual levels of these organic solvents in the tablet cores and film coats are critical, as beyond permissible limits, they are likely to cause undesirable side effects or alter some kind of physicochemical property of the active pharmaceutical ingredient. Hence it becomes necessary to limit the amount of these residual solvents, which can be called organic volatile impurities to certain levels within the ICH-prescribed limits[3]. The most sensitive among the methods for monitoring the amount of residual solvent in the marketed solid dosage formulations is the gas chromatographic method. Literature survey on residual solvent testing in active pharmaceutical ingredients and coated tablets cited gas chromatographic methods for the determination of organic volatile impurity. The objective

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of the present study was to develop a method for identification and quantification of isopropyl alcohol and dichloromethane by gas chromatographic method and apply the same for its determination in marketed formulations using helium as the carrier gas. Dichloromethane is used in the basic drug manufacture as a solvent and more precisely, in coating process. A gas chromatograph with headspace sampler equipped with flame ionization detector (FID), was used for the study. A general-purpose capillary column Elite-624 consisting of 6 % cyanopropylphenyl and 94 % dimethyl polysiloxane stationary phase with 0.53 mm internal diameter, 30 meter length and film thickness of 3 µm was used. Analytical grade isopropyl alcohol and dichloromethane (Merck) were used.

In headspace sampling the sample (either a gas, a liquid or a solid) is placed into the headspace vial, which is closed immediately and equilibrated. An aliquot is then withdrawn from the closed vial and transferred directly to the gas chromatographic system. The headspace sampling is an automatic sampler for headspace analysis[4].

Flame ionization detector is mass sensitive and used for the destructive analysis of organic compounds. As the sample enters the detector, it is mixed with hydrogen and burn in air, thereby generating ions. The ions are collected and measured by the detector, with their concentration proportional to the amount of compound present. Ion collected is enhanced by a polarized electric field that is created by applying a negative voltage to the jet tip.

EXPERIMENTAL

Isopropyl alcohol and dichloromethane (E. Merck) were purchased and used as such.

Gas chromatography Claus 500 and headspace sampler TurboMetrix 16 Perkin-Elmer with capillary column Elite-624 consisting of 6 % cyanopropylphenyl and 94 % dimethyl polysiloxane stationary phase with 0.53 mm internal diameter, 30 meter length and film thickness of 3 µm were used.

Chromatographic condition: Column: Elite-624 (30 meter, 0.53 mm ID, 3 µm df) (6 % cyanopropylphenyl - 94 % dimethyl polysiloxane); carrier gas: helium; flow rate: 1.0 mL/min; injector temperature: 190 ºC; split ratio: 1:10; oven program: initial 45 ºC hold for 5 min, Increase @ 15 ºC/min up to 200 ºC, hold for 5 min; detector temperature: 260 ºC; air gas flow - 450 mL/min; hydrogen gas flow - 45 mL/min; run time: 20 min.

Headspace sampler condition: Oven temperature: 85 ºC; needle temperature: 110 ºC; transfer line temperature: 90 ºC; thermostat period: 30 min; pressurize time: 2.0 min; inject time: 0.05 min; withdraw time: 0.02 min; GC cycle time: 30 min; capillary pressure: 15 psi.

Preparation of standard stock solutions: Transfer 10 mL of water in a 100 mL volumetric flask, weigh accurately about 500 mg of isopropyl alcohol and 60 mg of dichloromethane and transfer into the flask. Make up to the mark with water and mix.

Standard preparation: Transfer 0.5 mL of standard stock solution in a headspace vial, add 1.5 mL of water and seal.

Test preparation: Weigh accurately about 500 mg of sample and transfer into a headspace vial, add 2 mL of water and seal.

Blank preparation: Take 2.0 mL of water in a headspace vial and seal.

Procedure: Analyze blank preparation in single, standard preparation in triplicates and test preparation in duplicates on a GC-HS-FID System.

Calculations: Calculate the concentration (% w/w) of isopropyl alcohol (IPA) and dichloromethane (DCM), using the following formula:

$$\text{Concentration of IPA (\% w/w)} = \frac{AT_1 \times Ws_1 \times 0.5 \times 2 \times P_1 \times 100}{AS_1 \times 100 \times 2 \times W_T \times 100}$$

where, AT_1 = Average area of isopropyl alcohol peaks in test preparation, AS_1 = Average area of isopropyl alcohol peaks in standard preparation, Ws_1 = Weight of standard isopropyl alcohol in mg, W_T = Weight of sample in mg, P_1 = Purity of standard isopropyl alcohol (%).

$$\text{Concentration of DCM (\% w/w)} = \frac{AT_2 \times Ws_2 \times 0.5 \times 2 \times P_2 \times 100}{AS_2 \times 100 \times 2 \times W_T \times 100}$$

where, AT_2 = Average area of dichloromethane peaks in test preparation, AS_2 = Average area of dichloromethane peaks in standard preparation, Ws_2 = Weight of standard dichloromethane in mg, W_T = Weight of sample in mg, P_2 = Purity of standard dichloromethane (%)

RESULTS AND DISCUSSION

Specificity: Specificity has been established by injections of isopropyl alcohol and dichloromethane individually. The resolution obtained between the peaks was 3.4. Also no peaks were observed in injections of blank (water). Chromatograms of blank (water) and standard isopropyl alcohol and dichloromethane are presented in Figs. 1 and 2.

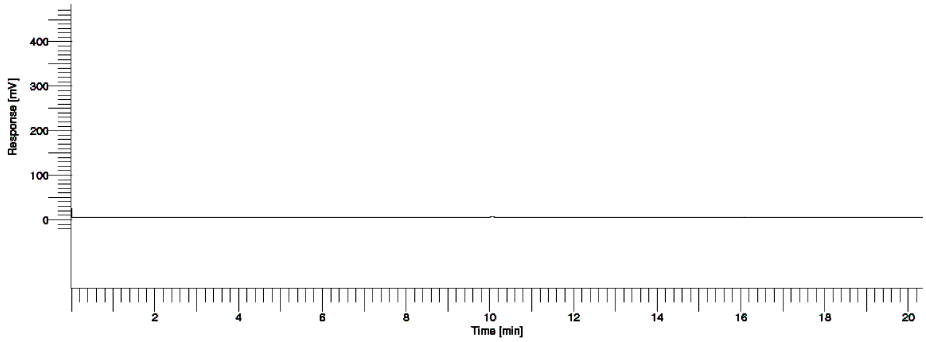

Fig. 1. Chromatogram of blank

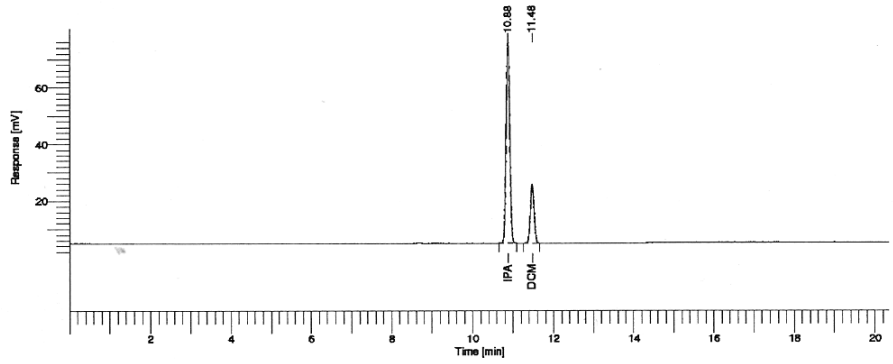

Fig. 2. Chromatogram of standards

System precision: System precision has been demonstrated by 6 replicate injections of standard solutions at the working concentration. The standard solution is prepared at the working concentration and analyzed as per method. The system precision of the purposed method is expressed in the term of % RSD of the data. The RSD was found out to be less than 10 %. All values are listed in Table-1.

TABLE-1
SYSTEM PRECISION

S. No.	Isopropyl alcohol	Dichloromethane
	Area	Area
1	493921.30	137656.64
2	458708.59	130126.11
3	480263.45	130762.28
4	471078.93	116279.94
5	453486.76	116911.88
6	464037.16	108775.48
Mean	470249.37	123418.72
Standard Deviation	14927.13	11039.57
% RSD	3.17	8.94

Method precision: Method precision has been demonstrated by separately analysing one batch of sample 6 times (as per the method). The method precision of the proposed method is expressed in the term of % RSD of the data. RSD was found to be less than 15 % (calculated only for residual solvent). All values are listed in Table-2.

Linearity and range: The method has been shown to be linear by a plot of 6 points in the range LOQ-120 % of specification limits. This has been confirmed by appropriate statistical methods. The linearity curve is drawn by plotting concentration *vs.* peak area response and from the linearity curve the regression value is determined

TABLE-2
METHOD PRECISION

S. No.	Isopropyl alcohol	Dichloromethane
	% (w/w)	% (w/w)
1	0.5571	0.0624
2	0.5766	0.0660
3	0.5521	0.0678
4	0.5592	0.0665
5	0.5400	0.0659
6	0.5500	0.0712
Mean	0.5558	0.0666
Standard Deviation	0.0122	0.0029
% RSD	2.2000	4.3300

for each compound. Correlation coefficient for each residual solvent was found to be more than 0.99. The results are shown in Table-3. Linearity curves are shown in Figs. 3 and 4.

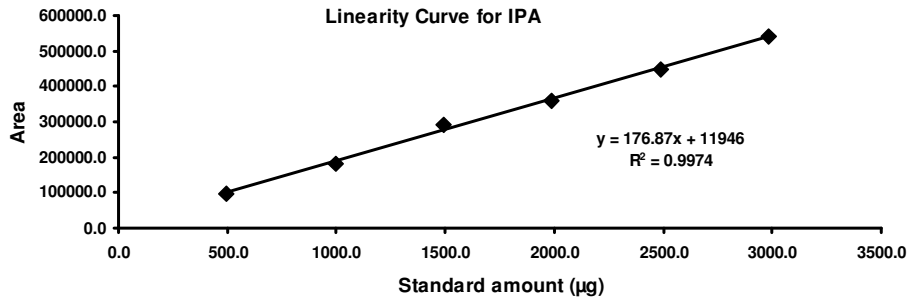

Fig - 3 Linearity curve of isopropyl alcohol (IPA)

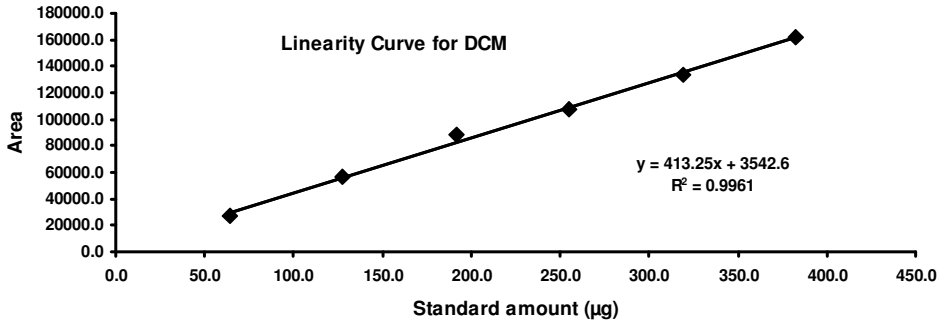

Fig - 4 Linearity curve of dichloromethane (DCM)

TABLE-3
LINEARITY AND RANGE

Compound	Linearity range (μg)	Regression coefficient (R^2)	Retention time (min)
Isopropyl alcohol	500-3000	0.9974	10.88
Dichloromethane	60-400	0.9961	11.47

Ruggedness: Ruggedness has been established by separate 6 analyses of single batch of sample, prepared by 2 different analysts on different days. The ruggedness of the purposed method is expressed in the term of % RSD of the all data. Overall RSD of residual solvents were found out to be less than 15 %. All values are listed in Table-4.

TABLE-4
RUGGEDNESS

Compound		Isopropyl alcohol	Dichloromethane
	S. No.	% (w/w)	% (w/w)
1st day	1	0.5571	0.0624
	2	0.5766	0.0660
	3	0.5521	0.0678
	4	0.5592	0.0665
	5	0.5400	0.0659
	6	0.5500	0.0712
2nd day	1	0.5729	0.0579
	2	0.5457	0.0556
	3	0.5731	0.0585
	4	0.5675	0.0586
	5	0.5612	0.0584
	6	0.5638	0.0601
	Mean	0.5599	0.0624
	Standard deviation	0.0115	0.0049
	% RSD	2.0600	7.8900

Accuracy: For accuracy studies, known amount of residual solvent standards were spiked into the placebo at about 50, 100 and 150 % of specification limits in triplicate. The recoveries have been calculated as given in the Table-5. The average recoveries were calculated to be 101.63 and 93.75 % for isopropyl alcohol and dichloromethane, respectively. So, it may be concluded that the method is accurate.

Limit of detection (LOD) and limit of quantification (LOQ): The limit of detection of an analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessary, quantified as an exact value. To define a limit of detection, the analyst must determine the minimum concentration of an analyte, which could be observed in a sample. The limit of quantification is the

TABLE-5
PERCENTAGE RECOVERY

Compd.	Level of spiking (% w/w)	Spiked amount (% w/w)	Recovered amount (%w/w)	Recovery (%)	Average recovery (%)
Isopropyl alcohol	0.25	0.24870	0.25280	101.64	101.63
	0.25	0.24870	0.26550	106.75	
	0.25	0.24870	0.24420	98.19	
	0.50	0.50070	0.55700	111.24	
	0.50	0.50070	0.57660	115.15	
	0.50	0.50070	0.55210	110.26	
	0.75	0.74620	0.67260	90.13	
	0.75	0.74620	0.70030	93.84	
	0.75	0.74620	0.65300	87.51	
Dichloromethane	0.03	0.03189	0.02741	85.95	93.75
	0.03	0.03189	0.02862	89.74	
	0.03	0.03189	0.02599	81.49	
	0.06	0.06290	0.06236	99.14	
	0.06	0.06290	0.06597	104.88	
	0.06	0.06290	0.06782	107.82	
	0.09	0.09569	0.08352	87.28	
	0.09	0.09569	0.09176	95.89	
	0.09	0.09569	0.08765	91.59	

lowest amount of an analyte in a sample, which can be quantitatively determined with precision and accuracy. LOD and LOQ have been established on the bases of S/N ratio (signal to noise ratio) by 6 injections at LOD level and 6 injections at LOQ level. The S/N ratio was found to be more than 3 for LOD and more than 10 for LOQ. The RSD was found out to be less than 10 %. The limits of detection for isopropyl alcohol and dichloromethane of the proposed method are 0.05, 0.006 % (w/w), respectively. The limits of quantification for isopropyl alcohol and dichloromethane are 0.1, 0.012 % (w/w), respectively in Table-6.

TABLE-6
LIMIT OF DETECTION AND LIMIT OF QUANTIFICATION

LOD			LOQ		
Compound	Std (µg)	% RSD	Compound	Std (µg)	% RSD
Isopropyl alcohol	0.050 % w/w	8.03	Isopropyl alcohol	0.100 % w/w	3.53
Dichloromethane	0.006 % w/w	8.51	Dichloromethane	0.012 % w/w	8.73

Robustness: Robustness has been established by analysing sample in triplicate as per the proposed method and by changing the carrier gas flow rate by + 10 % of the original value. The robustness of the purposed method is expressed in the term of % RSD of the all data. Overall RSD calculated only for residual solvents were found to be less than 15 %. All values are listed in Table-7.

TABLE-7
ROBUSTNESS

Compound S. No.	Isopropyl alcohol (% w/w)	Dichloromethane (% w/w)
1	0.5153	0.0636
2	0.5114	0.0625
3	0.5212	0.0643
1	0.4686	0.0634
2	0.4220	0.0598
3	0.3843	0.0549
Mean	0.4705	0.0614
Standard deviation	0.0566	0.0036
% RSD	12.0400	5.7900

System suitability: System Suitability has been demonstrated by analyzed standard solution during validation study. The system performance was checked by the resolution and % RSD. The resolution between isopropyl alcohol and dichloromethane was 3.4 and RSD for residual solvents were found to be less than 10 %.

TABLE-8
SYSTEM SUITABILITY

Compound	Retention time	Resolution	Tailing factor	No. of theoretical plates	% RSD
Isopropyl alcohol	10.88	–	1.02	64607	3.17
Dichloromethane	11.47	3.4	1.01	70428	8.94

Conclusion

The developed method was found to be accurate, precise and specific for the estimation of isopropyl alcohol and dichloromethane. The preparation procedure for samples is rapid and very simple. In conclusion, the proposed method is adequate for the purpose of confirmatory analysis of isopropyl alcohol and dichloromethane in the dosage form.

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