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IDENTIFICATION AND QUANTIFICATION OF AN UNKNOWN PEAK IN RESIDUAL SOLVENT ANALYSIS BY GC USING RELATIVE RESPONSE FACTOR

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Key words:

Dimethyl ether, GC-HS unknown peak, Relative response factor

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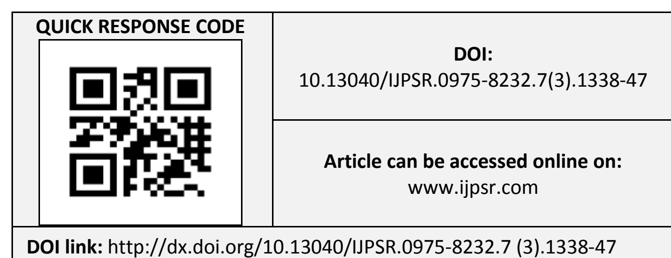
ABSTRACT: Organic solvents are integral part of chemical synthesis in pharmaceutical industry. These are commonly used as reaction media, in separation, purification of synthetic products and also for cleaning of equipment. Some of the solvents degrade to other solvents or unknown impurity either during synthesis or in analytical conditions. In this study, we have investigated formation of a trace level impurity, its identification and quantitation by successfully applying the concept of relative response factor (RRF) in GC-HS. The trace level impurity was identified as dimethyl ether (DME), formed due to interaction of strong acid and methanol. Unavailability of its commercial standard made the quantitation in drug substance challenging using gas chromatography. In this work, we have extended the concept of RRF for determination of DME in drug substances. The RRF of DME was established against other process solvents used in method of analysis. Application of RRF in quantitation of DME eliminates the requirement of its external standards during routine analysis at quality control laboratories.

INTRODUCTION: In the regulatory environment any unknown peak in chromatography attracts special attention because of increasing focus on safety and efficacy of drug substances and drug products. Presence of an extra or unknown peak in gas chromatographic analysis is not uncommon. These peaks may generally arise either due to thermal degradation of drug substance in chromatographic conditions [1, 2, 3, 4] or may be present in trace level in drug substance itself as solvent or impurity.



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Any peak whose formation can be established due to degradation of drug substance in GC-HS condition can be disintegrated. However, peaks arising due to presence of impurities in drug substance should be appropriately quantified.

During the analysis of residual solvents content in API-A, by head space gas chromatographic technique, an additional peak was observed before methanol peak, with signal to noise ratio (S/N) of 190. Since this was a new peak and not matching with any of the solvents used in synthetic process, considered as unknown peak. This peak was identified as dimethyl ether based on the mass number obtained by GC-MS with EI source. Its formation was postulated as acid catalyzed dehydration of methanol [5, 6, 7, 8] in presence of methanesulfonic acid and/or hydrobromic acid (HBr) used in synthetic process. However, presence

of unknown peak was investigated for both the possibilities and established that peak is not a degradant and rather forming in the synthetic process; hence required to quantify and control at appropriate level. Since DME is not readily available as external standard for quantitation, its determination in API-A was a challenging task. It can be quantified in drug substance by ^{1}H NMR technique which may not be feasible for most of the laboratories due to unavailability of NMR instrument. Concept of relative response factor is widely used in HPLC technique for determination of related substances. However, researchers have also worked towards determining the response factors of hydrocarbons using flame ionization detection (FID) [9, 10]. There are some theoretical approaches by which the FID response factors could be predicted in cases of unavailability of pure substances [11,12]. The accuracy of these theoretical methods in comparison with direct experimental determination of response factor lies in their predictive ability. L. Gonza´lez-Bravo *et al* [13] have presented a detailed group method approach to the estimation of response factors of unavailable substances in quantitative gas chromatography. However, in present study simple approach of establishing response factor by slope method[14] using a quantified DME solution was used and was applied to overcome challenges to quantify it using external standard in routine QC analysis.

Quantitative NMR is now established as a rapid and generic method for determining concentration, purity, reaction yield, and mixture composition. It was used to determine the assay of DME [15, 16, 17]. DME was synthesized in the laboratory and its assay was established by quantitative nuclear magnetic resonance (qNMR) comparing intensity of its proton signal with a proton signal of reference compound (THF) at a known concentration.

Dimethyl ether is not mentioned in ICH guidelines (Q3C) in the list of solvents to be controlled, however literature suggests that it has a low order of toxicity on both an acute and chronic basis [18, 19] According to ICH guidelines, the solvents with low toxicity potential can be controlled at 5000 ppm [20]. Based on above information, limit for DME can be proposed as not more than 5000 ppm. The diethylether (DEE) which is listed in ICH guideline as class-3 solvent (limit: 5000 ppm) is similar to DME, This also supports the proposed limit for DME. However, since DME is not a process solvent but a process impurity, which should be controlled at relatively lower level *e.g.* 500 ppm.

Experimental:

Chemicals & Reagents:

The investigated samples of API-A were obtained from Process Research Department, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd., Hyderabad, India. The DME was synthesized in the laboratory after identification by GC/MS. The LR grade methyl bromide, GC grade acetone, methanol (MeOH), dimethylformamide (DMF), tetrahydrofuran (THF), ethyl acetate (EtOAc) and toluene were purchased from Rankem (India). The deuterated solvent Dimethylsulphoxide-d6 was purchased from Aldrich Chemical Co., USA.

Instrumentation:

GC instrumentation:

The GC system used was Agilent 6890N consisting flame ionization detector (FID) and Head space sampler 7694. Data was processed using Empower3 software (Waters). Chromatographic separation was performed on DB-624 (Agilent) analytical column (30 m length x 0.53 mm internal diameter, 3.0 µm particle size). The GC oven temperature was initially held at 40 °C for 12 min, which was increased to 220 °C at the rate of 30 °C per minute and then held for 5 min at same temperature. High-purity helium was used as the carrier gas at a flow rate of 3.0 mL/min. Split injection was set at a split ratio of 4:1, and the injection temperature was 180 °C whereas detector temperature was at 240 °C. A total of 0.2 g of API-A powder was placed in a 20 mL headspace vial and 5 mL of DMF as diluent was added to it. The headspace vial was hermetically sealed using a silicone/PTFE septum and a magnetic cap and then incubated at 85 °C for 10 min. while agitating. The agitator speed was set at 250 rpm. A 3.0 mL loop 2.5 mL airtight syringe (Hamilton, Darmstadt, Germany) was used for headspace sampling, and the syringe temperature was maintained at 110 °C. The injection time was 1.0 min.

GC-MS Instrumentation:

The Agilent 7890A Gas chromatograph coupled with Mass selective detector (Agilent GC/MS/MS model 5979C, Agilent Technologies Inc., Santa Clara, CA, USA) with electron impact ionization (EI) source was used for identification of peak. The data acquisition was controlled by Chemstation software version D.02.00. The ion source temperature was set at 230/120 °C, Quadruple temperature 150 °C and MS was run in scan mode using the settings from the *atune.u* file with an electron multiplier offset of 200 eV.

Instrumentation for NMR analysis:
The assay of DME was performed by quantitative NMR technique. ^{1}H- NMR was performed on Varian Mercury plus 400 MHz NMR instrument at 25 °C in DMSO-d6. The ^{1}H chemical shift values were reported on the δ scale in ppm, relative to tetra methyl silane (TMS) (δ = 0.00 ppm). The NMR probe was tuned with the sample in place, and the 90° pulse width measured. The spectrum was recorded acquiring 16 scans with a 90° pulse and a 60-s relaxation delay. Spectra were Fourier transformed with 1 Hz of line broadening and zero-filling the FID's to 128 K points and carefully phased manually. Peaks of interest were integrated over a window of 32 times the peak width (full-width-at-half-height) after linear baseline correction between the edges of the integration window.

Preparation of solutions:
A solution of API-A was prepared at the concentration of 40 mg/mL in GC grade DMF. The solution of solvents were prepared by pipetting the appropriate volumes corrected for density (*d*) and diluted to get the concentrations equivalent to their respective ICH limits. The stock solutions THF(*d*;0.8833 g/mL), MeOH(*d*; 0.791 g/mL), EtOAc(*d* :0.895 g/mL), hexanes (*d*: 0.659 g/mL) and toluene(*d*: 0.867 g/mL) were prepared by diluting 190 µL of methanol, 22 µL of hexane, 280 µL of EtOAc, 40 µL of THF and 51 µL of toluene in a 25 mL volumetric flask and diluted up to the mark with DMF. The standard solution was prepared by transferring 1.0 mL of above stock solution into 50 mL volumetric flask and diluted up to the mark with DMF. Stock solution of DME solution was prepared by diluting 1.5 mL of 'DME solution in acetone' to 50 mL with DMF to get the concentration of approximately 5000 ppm.

Investigation of formation of DME Peak:
The DME peak could be an analytical artifact or could be potentially present in the API-A as impurity; hence it was investigated for both possibilities. Analytically, the formation of DME is possible during equilibration of GC-HS vial, whereas it can also form in manufacturing process during isolation or drying operation.

Method Validation:
The method for determination of DME and other residual solvents in API-A was appropriately validated according to the ICH guidelines [21]. The validation parameters were based on the following criteria: selectivity, response function (calibration curve), linearity, precision (repeatability and intermediate precision), accuracy, LOD and LOQ. The relative response factor of DME against process solvents was also determined as ratio of slope of DME calibration curve *vs.* slope of respective process solvent.

Relative response factor (RRF) of DME:
The response factor accounts for differences in the detector response between the analyte and standard. It is measured by injecting a series of mixture containing known amounts of analyte and standard. Since there were challenges to quantify DME using its external standard in routine QC analysis, due to high volatility and existence in gaseous state of this compound, its RRF was established against other process solvents. The RRF was calculated as ratio of slope obtained from linearity plot of DME v*s.* of individual solvent, using formula 1. The value of slope obtained from the linearity was used for calculation.

$$RRF = \frac{Slope\ of\ DME}{Slope\ of\ individual\ solvent} \qquad (1)$$

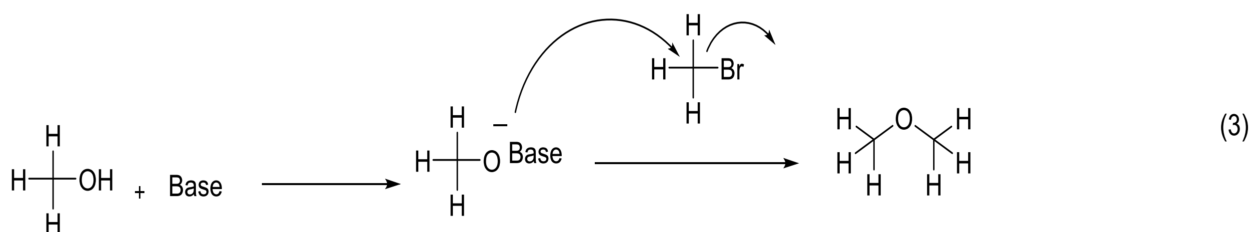
In the gas chromatographic determination of residual solvents by GC/GC-HS, RRF can't be applied directly since these are not area normalization methods. To calculate the content of DME in API-A, first the response factor of solvent was calculated as ratio of concentration *vs.* peak area response, then RRF was applied to area of

DME obtained in test sample as mentioned in formula 2.

$$Content(ppm) = \frac{Content\ of\ solvent\ standard(ppm) \times Area\ of\ DME\ in\ test\ sample}{Average\ area\ of\ solvent\ standard \times RRF\ of\ DME} \quad (2)$$

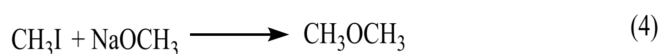
RESULTS AND DISCUSSION:

Identification of unknown peak by GC-MS analysis: The fragmentation pattern and mass number of extra peak matched with DME when checked with library data in GC-MS analysis(**Fig.1**), which proved that it could be dimethyl ether (DME; *i.e.* 46). The manufacturing process of API-A involves conversion of sulfonic acid salt of crude API to hydrobromic acid salt. This reaction was carried out in methanol medium. Literature reveals that the acid catalyzed condensation of alcohols is possible *via* SN^1 mechanism; however primary alcohol and methanol will proceed via SN^2 mechanism since they have highly unfavorable carbocation. The API-A is prepared in the form of hydrobromide salt using methanol as a solvent. Literature suggests that, in presence of acid, alcohol can react to form corresponding alkyl ether.



To confirm the identity of peak experimentally, DME was prepared by mixing methyl iodide & sodium methoxide in methanol. This solution was injected in GC-MS, mass and fragmentation pattern of DME matched with library, which conforms the presence of dimethyl ether. Portion of this solution was also injected in method of residual solvents in API by GC-HS and retention time of DME was compared with the unknown peak in the batch analysis; which confirmed that the unknown peak is DME.

Since the identity of unknown peak is now confirmed as DME, analytical standard of it was required for further studies. But unavailability of analytical standard is an additional complexity; hence the only choice left is to synthesize in laboratory. A 20% w/w solution of sodium methoxide in 50 mL DMF was prepared and slowly added 3.82 g of methyl iodide to it. The liberated dimethyl ether gas was purged into acetone maintained at -50 ºC.



$$CH_3I + NaOCH_3 \longrightarrow CH_3OCH_3 \quad (4)$$

The formation of DME was confirmed by GC/MS and quantitation was quantified by qNMR.

Investigation of formation of DME peak: Though the peak was confirmed as DME, it is imperative to establish its source of formation. API-A is an HBr salt and any residual amount of methanol present in it may lead to two possibilities of formation of DME could be explained as below.

A. Due to GC-HS condition

During equilibration of GCHS vial (containing API-A material) in head space condition while analyzing for residual solvent content.

B. During synthetic process

While drying of material in manufacturing process

Following studies were planned to establish either of above hypotheses.

A. Experiments pertaining to GC-HS Conditions

i. In presence of excess methanol:

Assuming excess methanol may react with HBr during vial equilibration and give rise to DME peak. When methanol was spiked into API-A at three different levels *i.e.* 1500 ppm, 3000 ppm and 4500 ppm with respect to nominal analyte concentration, no change in the level of DME peak was observed. Percentage recovery of methanol

was calculated and found between 95-102%. Hence the possibility of formation of DME during vial equilibration due to residual methanol could be ruled out.

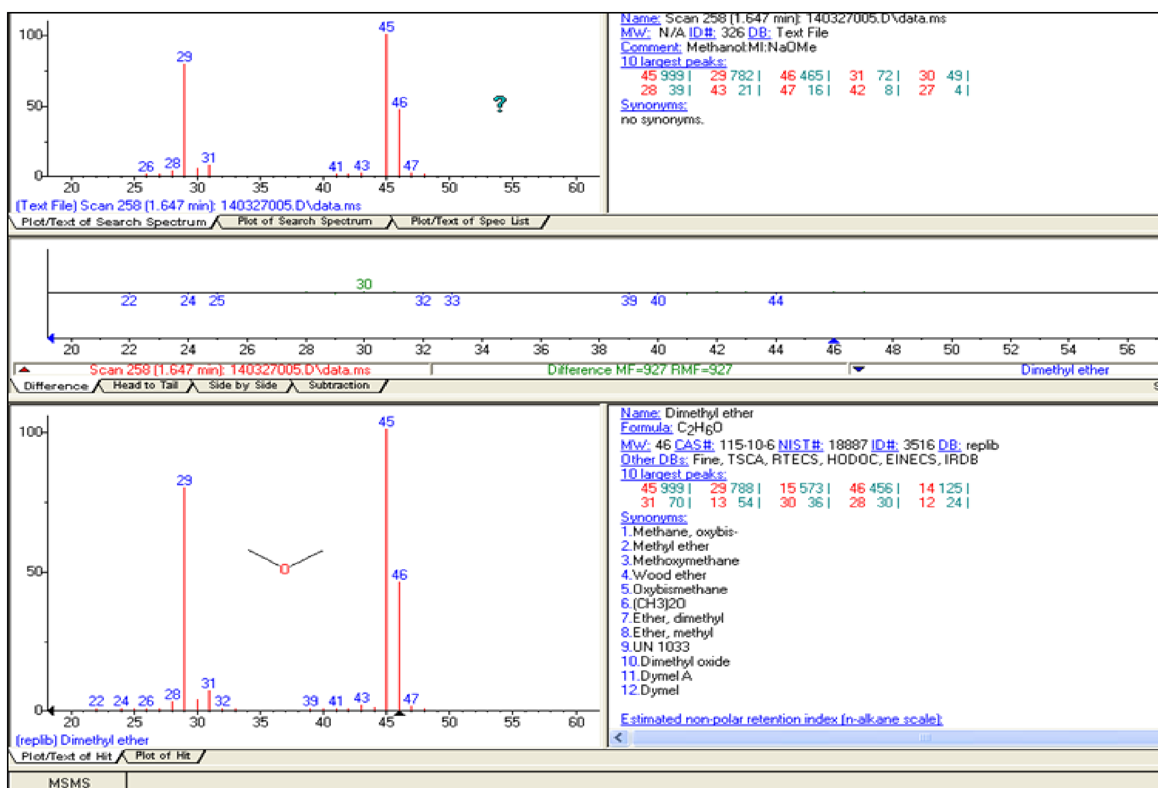


FIG 1: GC-MS PATTERN OF UNKNOWN PEAK IN TEST SAMPLE AND ITS COMPARISON WITH LIBRARY DATA SHOWING THE UNKNOWN PEAK AS DME

ii. **Analysis after neutralization in GCHS conditions:**

Assuming that the trace level of free HBr is present in API-A, which may react with methanol to form DME during vial equilibration, neutralization of API-A solution should eliminate the DME. To the test solution dilute triethyl amine was added and injected into GC-HS. As such API-A was also injected separately as control experiment. The DME peak appeared at similar intensity even after addition of base, which eliminates the possibility of formation of DME in analytical conditions and confirms that it was already present in the API-A.

B. Experiments pertaining to API drying conditions

To understand the impact of drying procedure on level of DME peak, small portion of two different batches of API-A were dried at higher temperature than the usual, once again. Hypothesis was that DME formed during synthetic process might have trapped into the API-A. Being a low boiler solvent (boiling point; less than -20 °C), it should evaporate at higher temperature. A portion of API-A was grinded before drying to provide more surface area to API-A and facilitate effective removal of DME. Hence the test sample was subjected to grinding and drying followed by analysis as mentioned below (**Fig.2**) and peak area response of DME was compared before and after the drying. As such API-A was also injected separately as control experiment.

i. Ground and injected
ii. Ground, dried at 90 °C and injected
iii. API taken as such, dried at 90 °C and injected

It is observed that the intensity of DME didn't change only by grinding, but increased when additionally dried at elevated temperature *i.e.* 90 °C for 2 h. Based on this observation; further drying studies were planned by keeping drying temperature as 65 °C. Portion of samples were withdrawn at different intervals, analyzed in GC-HS and change in peak response of DME and methanol peak was compared. Results are summarized in **Table 1**. The presence of DME

peak in this experiment proves that it is formed during drying operation.

TABLE 1: COMPARISON OF PEAK RESPONSE OF METHANOL *VS*. DME

S.N.	Interval (hours)	Peak area by GC-HS(Drying at 65 °C)			
		As Such API		grinded API	
		DME	MeOH	DME	MeOH
1	0	28.96194	72.03806	28.96194	72.03806
2	6	36.52457	63.47543	37.10386	61.89614
3	9	37.16647	61.83353	38.08694	59.91306
4	12	41.40447	56.59553	40.75827	54.24173

Quantitation of DME:

Quantitation of DME solution in acetone was performed by quantitative NMR using Tetrahydrofuran as internal standard (IS) and deuterated dimethylsulfoxide (DMSO-d6) as solvent. The signal intensity of a known amount of internal standard was compared to the area of the peaks originating from the API-A. Content of DME was calculated using below mentioned formula 5.

$$D_a = \frac{I_x}{I_{std}} * \frac{N_{std}}{N_x} * \frac{M_x}{M_{std}} * \frac{m_{std}}{m} * P_{std} \quad (5)$$

D_a = Assay of the DME (in %w/w)

I_x = Mean Integral value of the analyte ^{1}H signal (doublet) obtained at 3.2 ppm

I_{std}= Integral value of the ^{1}H signal of THF IS obtained at 3.6 ppm

N_{std} = Number of protons for the THF IS

N_x = Number of protons for the analyte ^{1}H in drug

M_x = Molar mass of the analyte (For DME 46.07 gm/mole)

M_{std} = Molar mass of the THF IS (72.11 gm/mole)

m_{std} = Weight of the THF IS. (in mg)

m = Taken weight of the analyte (in mg)

P_{std} = Assay of the THF IS (99.90%)

All the six protons of DME are in same environment appears as single peak at 3.2 δ ppm. THF shows signal at about 3.6 δ ppm, corresponds to two protons used as reference peak for the assay determination of DME. Assay of DME was calcualted using formula 1. Assay of DME in acetone solution is obtained as 0.69%w/w

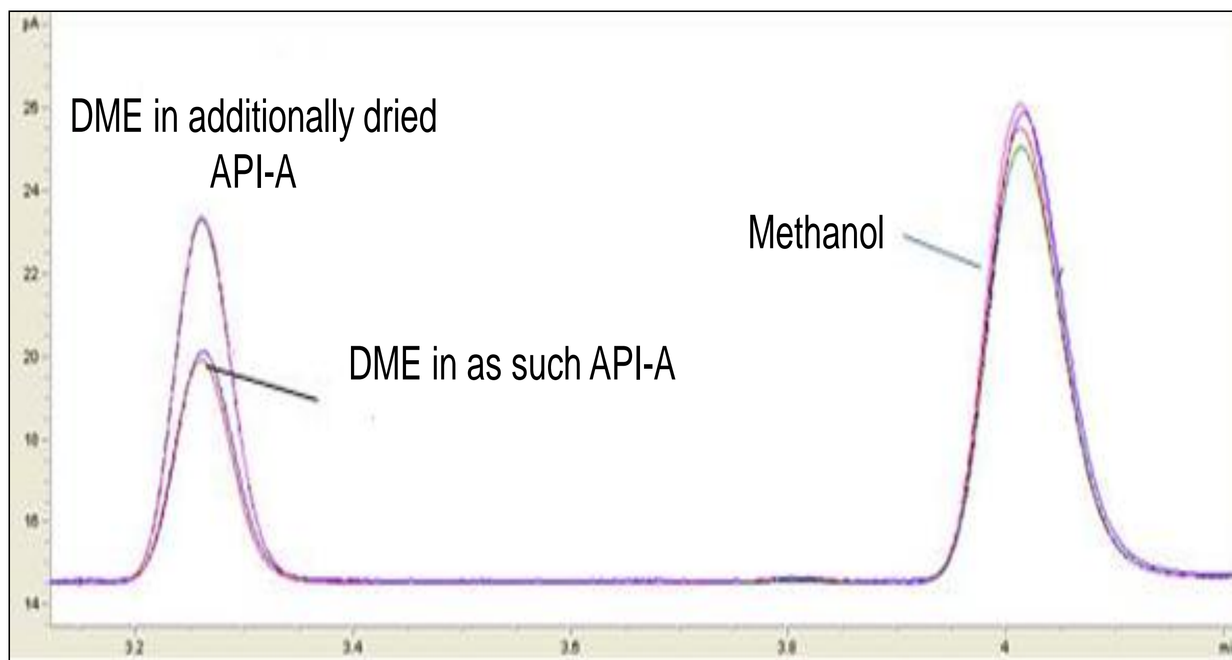


FIG.2a: OVERLAID CHROMATOGRAM OF API SAMPLE BEFORE AND AFTER ADDITIONAL DRYING; SHOWS IMPACT OF DRYING ON RESPONSE OF DME IN API-a

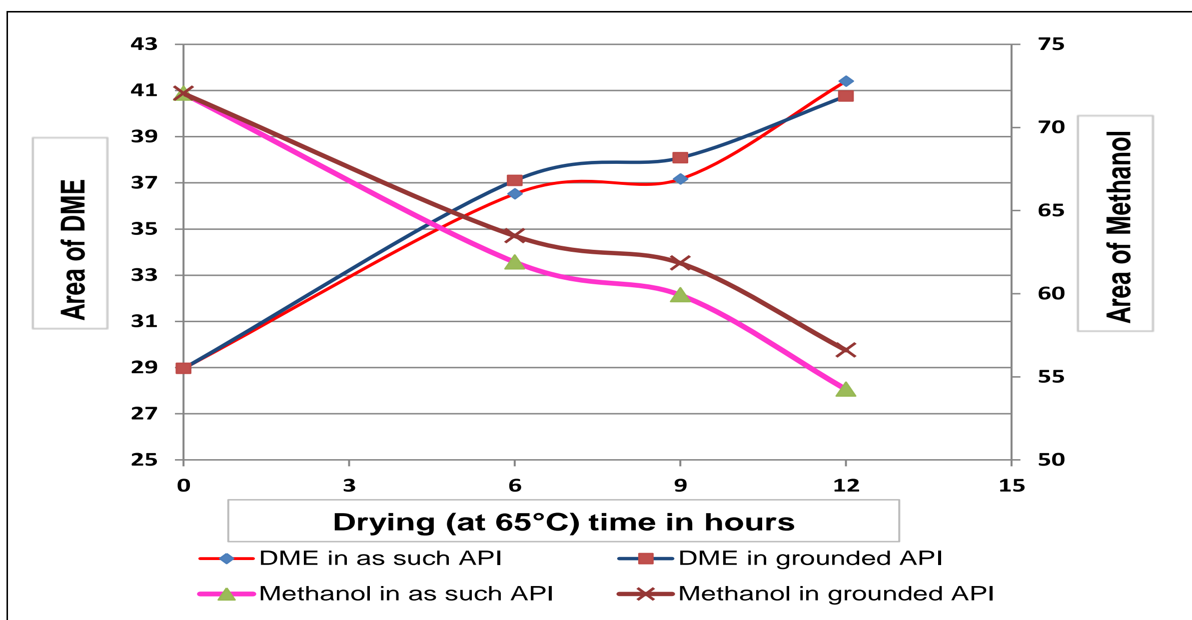


FIG 2b: GRAPHICAL REPRESENTATION OF CHANGE IN THE RESPONSE OF DME vs. METHANOL IN EXTENDED DRYING.

Figure 3a

DME

Figure 3b

THF

Dimethyl ether

FIG 3:a) NMR SPECTRA OF DME SOLUTION IN ACETONE AND DME IN PRESENCE OF INTERNAL STANDARD THF, b) NMR SPECTRA OF DME IN AND INTERNAL STANDARD

3.4. Method validation:

The system suitability, linearity, precision, recovery, solution stability was evaluated during method validation. Limit of detection and quantitation was established for solvents including DME. Specificity of DME was ascertained by injecting it along with process solvents and resolution between solvents was evaluated. (**Fig. 4**). The percent RSD for peak areas of the solvents namely Methanol, THF, EtOAc, hexanes, toluene and DME in the study of the repeatability was less than 4.8%.

Results for intermediate precision are within 4.9 %. These results demonstrate that the method is precise (**Table 3**). Limit of detection, limit of quantitation values for DME and other process solvents are reported in **Table 2**. The recoveries at LOQ level are in the range of 91.7–107%. The percentage RSD for content DME and process solvents at limit of quantitation level are within 4.6%. Recovery of DME and other solvents was studied at their respective allowable limit and found ranged from 94.1 to 107.9% at three different levels as mentioned in **Table 3**.

TABLE 2: LOD, LOQ, AND REGRESSION

Solvent	LOD (µg/mL)	LOQ (µg/mL)	LOQ Accuracy	Regression equation		Correlation	RRF
			% Recovery	Slope	Intercept		
DME	0.23	0.69	105.2	2.17	-2.21	0.9998	-
Methanol	8.2	25.0	97.4	0.085	4.83	0.9990	25.5
THF	2.4	7.3	107.2	0.31	2.58	0.9999	6.6
Ethyl acetate	5.8	17.6	104.1	0.16	8.03	0.9998	12.8
Hexane	1.0	3.0	103.8	2.23	9.16	0.9996	-
Toluene	1.6	4.8	91.8	0.18	1.77	0.9993	-

TABLE 3: PRECISION AND ACCURACY OF DME AND OTHER SOLVENTS

Compound	Precision	Method Precision	Intermediate precision		Recovery		
	LOQ		Day1	Day2	50	100	150
DME	4.6	2.3	3.1	3.7	96.1	98.3	95.4
Methanol	4.2	3.6	2.9	4.2	98.5	94.4	94.1
THF	3.8	2.9	2.7	2.4	101.0	100.5	98.4
Ethyl acetate	2.8	3.9	2.6	2.9	103.2	99.8	102.2
Hexane	4.0	2.0	3.1	3.5	107.9	100.4	101.1
Toluene	3.6	1.6	3.3	2.1	103.6	101.7	99.1

The DME solution was prepared at five different concentration levels. Similarly, the solution of other process solvents namely ethyl acetate, methanol, hexanes, THF and toluene were also prepared at five different concentration levels. The linearity curve was plotted separately for DME and each solvent taking the concentrations of X-axis and peak area response on Y-axis. Slope and intercept for the linearity plots were calculated and presented in **Table 2.** The correlation coefficient obtained was >0.99 for all the components, which confirmed good linearity between peak areas and concentration.

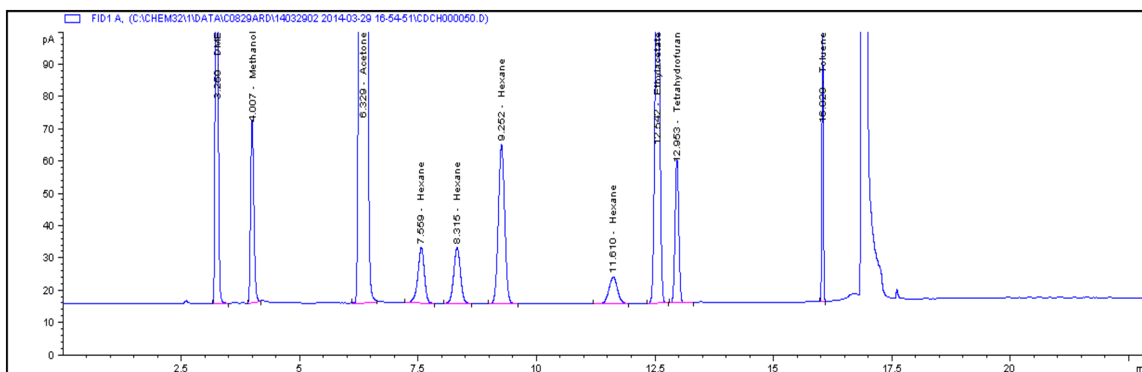


FIG. 4: TYPICAL SPECIFICITY CHROMATOGRAM OF DME WITH OTHER PROCESS SOLVENTS

Relative response factor (RRF) of DME:
Relative response factor was established against the three process solvents *i.e.* ethyl acetate, methanol and THF. The relative response factor was calculated as ratio of slope obtained from linearity plot of DME v*s.* individual solvent, using formula 1. The value of slope obtained from the linearity was used for calculation. The RRF against methanol, THF and ethyl acetate was calculated as 25.5, 6.6 and 12.8 respectively. The content of DME was calculated in API-A is by applying RRF as well as in conventional external standard technique and the content obtained was compared. Values obtained by both the methods match closely to each other confirm the correctness of RRF. Data is presented in **Table 6**.

TABLE 5: RESULTS OF SPECIFICITY

Solvent name	Retention time (min.)	Resolution
Dimethyl ether	3.3	-
Methanol	4.0	6.7
Hexane	7.6, 8.3, 9.3,11.6	19.2
Ethyl acetate	12.5	3.8
THF	13.0	2.6
Toluene	16.0	31.0

TABLE 6: CONTENT OF DME

API Batch	%w/w Content of DME by			
	External standard Method	Applying RRF against		
		Methanol	THF	Ethyl acetate
Batch 1	100.3	103.4	101.4	93.3
Batch 2	31.4	30.2	30.1	29.6

CONCLUSION: The unknown impurity observed before methanol peak at S/N ratio of 190 was identified by GC/MS. It was synthesized in laboratory and characterized as DME based on the mass and experimental data. Its RRF was established against the three different solvents *i.e.* methanol, ethyl acetate and THF as 25.5, 12.8 and 6.6 respectively. The DME is successfully quantified using a validated GC method using concept of relative response factor. The correctness of RRF was also established by comparing the content of DME by direct quantitation using external standard of DME. The concept of applying RRF can be extended to several other commercially unavailable solvents/reagents which are observed in GC-HS analysis. Applying RRF for quantitation, eliminates the requirement of external standards of DME and simplifies the use of method at quality control laboratories.

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AUTHORS' STATEMENT:
Competing Interests: The authors declare no conflict of interest.

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