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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF CLASS-2 RESIDUAL SOLVENTS IN LULICONAZOLE BY HS-GC

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Keywords:

Headspace gas chromatography, flame ionization detector, Luliconazole and Residual solvents

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ABSTRACT: A simple headspace gas chromatographic (HS-GC) method has been developed and validated for the simultaneous determination of residual solvents like methanol, methyl isobutyl ketone, cyclohexane and toluene in luliconazole by Flame ionization detector (FID). The separation was achieved on 30 m long DB-624 column, 0.53 mm in inner diameter, and 3.0 µm in film thickness. The headspace and chromatographic parameters like flow rate and oven temperature are optimized to enhance sensitivity and chromatographic resolution. Dimethyl sulfoxide is used as diluents, equilibration temperature of 80 °C for 5 min, programmed temperature in the range of 35 °C to 210 °C and nitrogen as the carrier gas was used. The developed headspace gas chromatographic method offers good symmetry and resolution for all the residual solvents. The proposed was found to be suitable for the determination of 4 different residual solvents. Validation results indicated that the method is specific, linear, precise, accurate, rugged, and robust, where recoveries ranged between 90-110%.

INTRODUCTION: Residual solvents are defined as the volatile organic chemicals which are used or produced in the preparation of drug substances or excipients. These solvents are not totally removed during the synthesis of drug substances, and they do not have any therapeutic activity. Sometimes in the synthesis of drug substances, some amount of these residual solvents may remain in the product, so it is necessary to estimate the amount of these residual solvents in drug products.

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Depending on risk assessment, the residual solvents are classified into 3 types:

Class-1: Solvents to be avoided

Class-2: Solvents to be limited

Class-3: Solvents with low toxic potency

Hence, the detection of residual solvents is possible in gas chromatography [1]. Nowadays, headspace analysis is essential in the detection of trace amounts in the sample. It is very hard to imagine an organic analytical laboratory without gas chromatography. It is the most popular technique for the analysis and separation of volatile compounds worldwide. Generally, the word "chromatography" was coined by Tswett. The development of the GC instrument was focused by Tswett, Martin, Synge and James.

Today gas chromatography has become a very important one, and its income was estimated up to $ 1 billion, and 30,000 instruments of GC are working annually [2]. Headspace is a separation technique in which volatile material that is estimated from the sample and injected into a gas chromatography for the analysis and separation. The sample compound in headspace does not depend on their volatility but also on their affinity of the sample phase. This process is generally described as the partition coefficient, and it is defined as the ratio of the concentration of molecules between 2 phases. The headspace technique is mainly affected by temperature, pressure, sample matrix, and equilibration time [3]. The chemical name of Luliconazole is 2-[(2E,4R)-4-(2,4-dichloro-phenyl)-1,3-dithiolan-2 ylidene]-2-(1,H-imidazole-1-yl). The chemical structure of Luliconazole is mentioned in **Fig. 1**.

It is an imidazole antifungal drug that is used as a topical cream medication used for the treatment of athlete's feet, jock itch and ringworm that is caused by *trichophyton rubrum, Microsporum gypsum* and *Epidermophyton floccosum* [4]. The exact mechanism of action of Luliconazole is to inhibit the enzyme lanosterol 14-demethylase synthesis, which results in decreasing the amount of ergosterol [5-6].

A literature survey has reported that several analytical techniques were found for the estimation of luliconazole by LC [7], RP-HPLC [8, 9], HPTLC [10, 11], TLC [11,] and UV [12, 13] methods. The aim of the present study was to determine residual solvents, mainly methanol, methyl isobutyl ketone, cyclohexane, and toluene in the pure drug of Luliconazole.

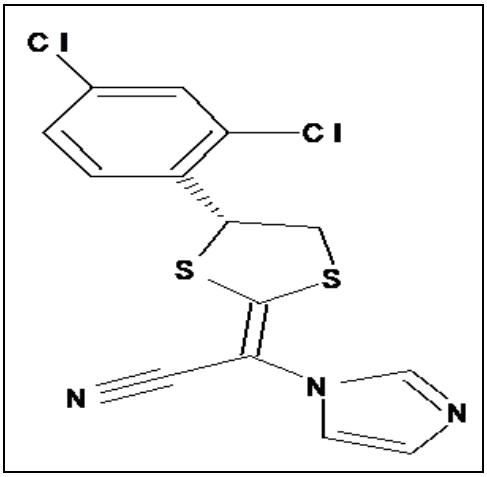


FIG. 1: CHEMICAL STRUCTURE OF LULICONAZOLE

MATERIALS AND METHODS:

Chemicals and Reagents: Luliconazole is received as a gift sample from Chandra labs, Hyderabad. Methanol (HPLC grade) obtained from Qualigens. Methyl isobutyl ketone, Cyclohexane, and Toulene obtained from the Sigma Aldrich and Dimethyl sulfoxide were obtained from Qualigens.

Instrument: The analysis was performed on Agilent gas chromatography model number 7697A headspace sampler using the DB-624 column and FID detector with nitrogen as a carrier gas. The chromatographic and Headspace conditions are mentioned in **Tables 1** and **2**.

TABLE 1: CHROMATOGRAPHIC CONDITIONS

Column	DB-624 Column, (30m × 0.53 mm) 3.0 µm
Initial oven temperature	60 °C
Initial Hold time	5.0 min
Carrier gas	Nitrogen
Flow	3 ml/min
Total runtime	15 min
Injector temperature	1500 °C
Detector temperature	2500 °C

TABLE 2: HEADSPACE CONDITIONS

Loop temperature	95 °C
Transfer line temperature	105 °C
GC Cycle time	20 min
Vial equilibration time	5 min

Preparation of Solutions:

Standard Stock-I Preparation: Weigh accurately about 500 mg of Methanol, 500 mg of Cyclohexane, 500 mg of Toluene, 500 mg of Methyl isobutyl ketone in 100 ml volumetric flask makeup to volume with diluent and shake well.

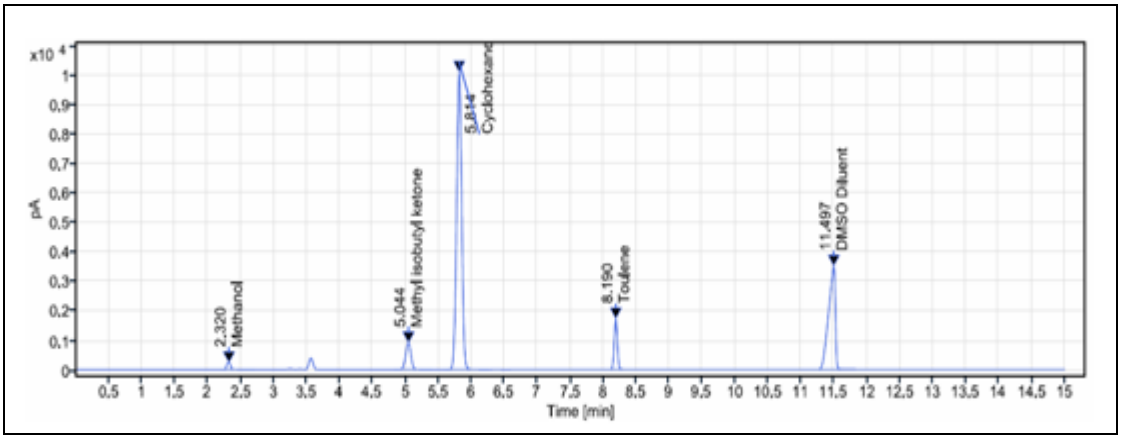
Standard Stock-II Preparation: Pipette out 1 ml of the above solution in 100 ml volumetric flask make up to the volume with diluent. Pipette 5 ml of above-prepared solution in headspace vial and seal the vial.

Test Sample Preparation: Weigh accurately about 50 mg of the test sample (Luliconazole API) and transfer into 50 mL volumetric flask add some amount of diluent, vortex it for 5 min. Then make up the volume with diluent and mix well. Pipette 5 ml of above-prepared solution in headspace vial and seal the vial.

Procedure: Prepared solutions are taken into 5 ml headspace vial, seal the vials with the help of

crimper. The prepared standard and sample solutions are subjected to headspace analysis.

Analytical Method Development: Several trails are carried for the development and the simultaneous estimation of residual solvents in luliconazole. Finally, a better separation was achieved by better resolution and good peak shape mentioned in **Fig. 2.**



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.320	1016.93	236.99	1.11		8242.91510	1.11486	1.00257
Methyl isobutyl ketone	5.044	5143.22	910.86	5.59	21.46970	17723.94723	0.95980	0.95005
Cyclohexane	5.814	54941.48	10119.68	59.70	5.17821	25533.16563	0.99303	0.99176
Toluene	8.190	5580.94	1715.54	6.06	20.37760	139412.66758	1.01035	1.00618
DMSO diluent	11.497	25344.68	3510.36	27.54	22.75405	51336.69462	0.64279	0.63843

FIG. 2: OPTIMIZED CHROMATOGRAM OF RESIDUAL SOLVENTS

RESULTS AND DISCUSSION:

Method Validation: [14] The method was validated for Linearity, Specificity, System suitability, Precision, Accuracy, Robustness, Ruggedness, LOD, and LOQ as per ICH guidelines.

Linearity: The linearity study of all residual solvents ranges from 25-150 ppm for methanol, cyclohexane, methyl isobutyl ketone and toluene (r^2>0.999) for the amount of solvent estimated in by the proposed methods was in good agreement.

The results are summarized in **Table 3.** The calibration graphs for all residual solvents are mentioned in **Fig. 3, 4, 5,** and **6**.

TABLE 3: DATA OF LINEARITY FOR RESIDUAL SOLVENTS

S. no.	Conc. (µg/ml)	Methanol	Methyl isobutyl ketone	Cyclohexane	Toluene
1	25	283.75	1351.01	10722.25	1490.10
2	50	545.42	2665.46	23715.31	2995.35
3	75	772.21	3832.06	35431.25	4235.52
4	100	986.52	4953.21	47375.78	5162.93
5	150	1472.87	7335.00	73116.38	7913.38

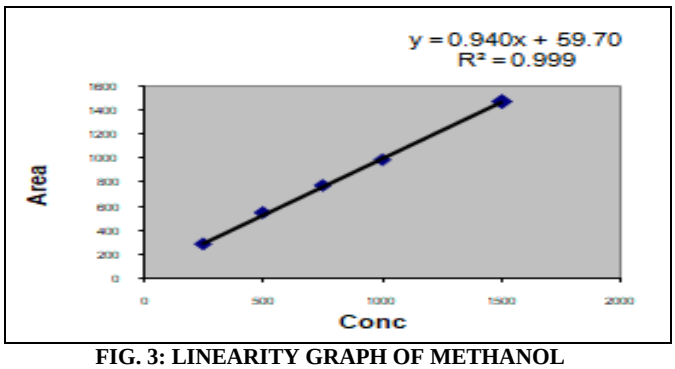


FIG. 3: LINEARITY GRAPH OF METHANOL

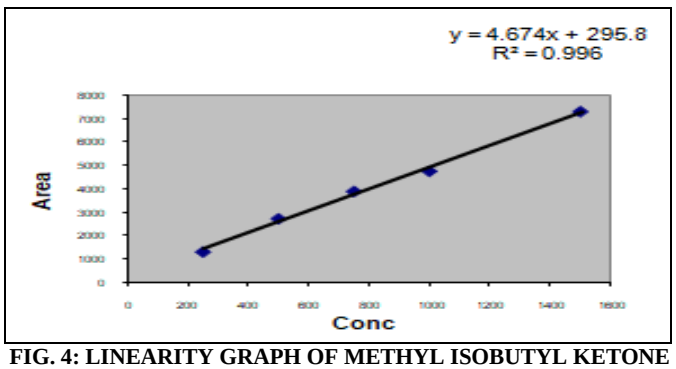


FIG. 4: LINEARITY GRAPH OF METHYL ISOBUTYL KETONE

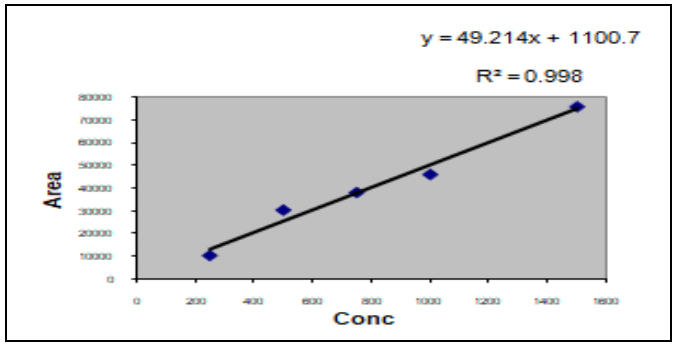


FIG. 5: LINEARITY OF CYCLOHEXANE

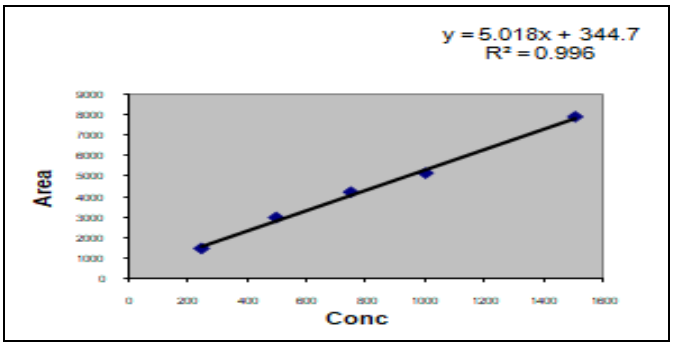
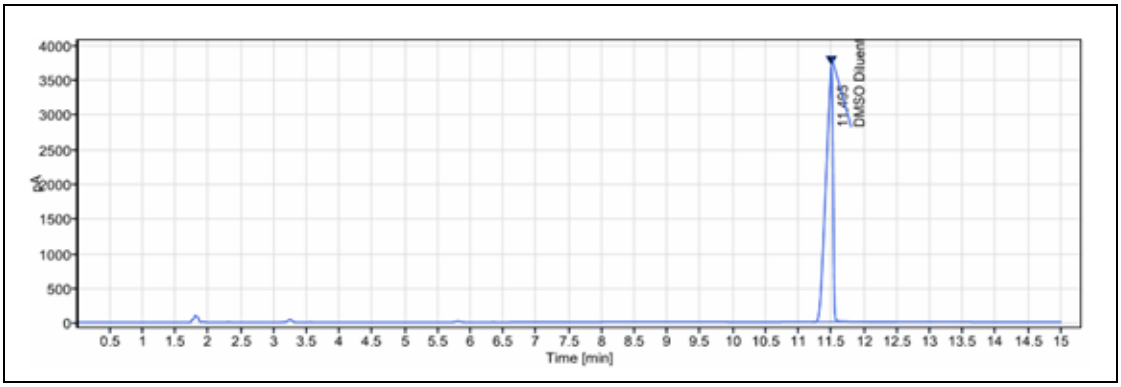


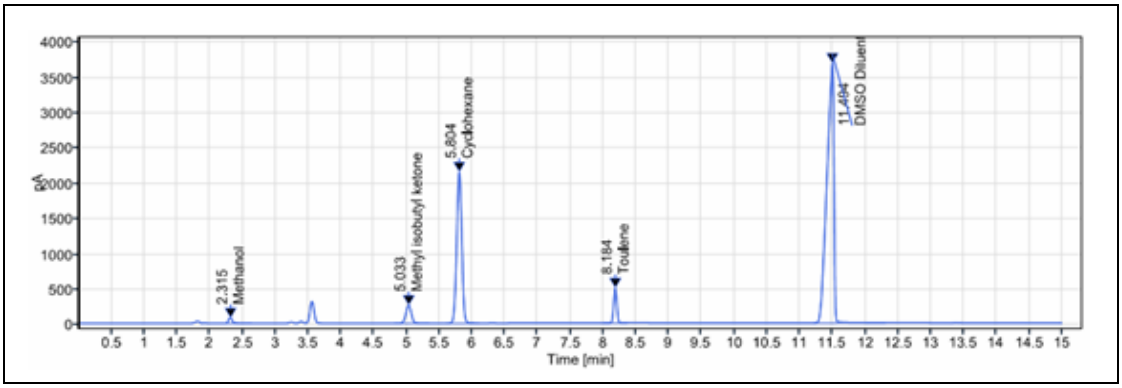
FIG. 6: LINEARITY GRAPH OF TOULENE

Specificity: Specificity was carried out by analyzing the non-interference of residual solvents. The first reagent blank was injected into headspace to record the chromatogram. Then, the standard solution of residual solvents was injected to record the chromatogram. Finally, the spiked sample is injected to chromatograms to record the chromatogram. The chromatograms of blank, standard solution, and spiked sample solution were shown in **Fig. 7, 8,** and **9,** respectively. The results for specificity were shown in **Table 4**.



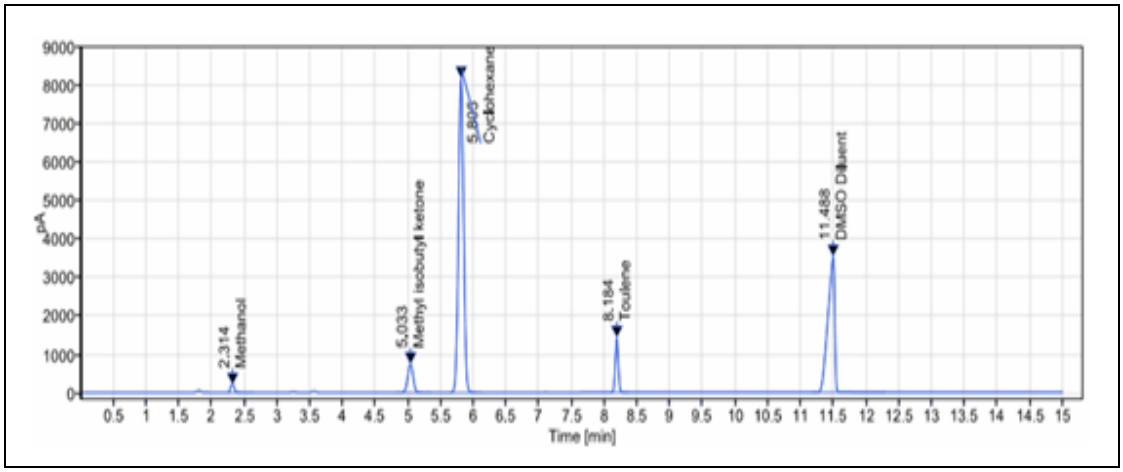
Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
DMSO diluent	11.495	27456.73	3686.22	100.00		47928.10869	0.63771	0.63402

FIG. 7: CHROMATOGRAM OF BLANK



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.315	305.85	73.37	0.72		8767.76030	1.12791	1.01687
Methyl isobutyl ketone	5.033	1454.49	254.36	3.44	21.65770	17525.84154	0.97606	0.96807
Cyclohexane	5.804	11575.97	2140.52	27.42	5.18064	25444.54111	1.0023	0.99704
Toluene	8.184	1617.07	495.13	3.83	20.45568	140767.56361	1.00620	1.00136
DMSO diluent	11.494	27269.27	3677.40	64.58	22.36406	48505.73054	0.63750	0.63355

FIG. 8: CHROMATOGRAM OF STANDARD SOLUTION



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.314	862.80	198.40	1.08		8004.90151	1.11599	1.00896
Methyl isobutyl ketone	5.033	4227.19	729.99	5.29	21.11733	17076.85377	0.96536	0.95672
Cyclohexane	5.805	44651.26	8154.94	55.88	5.13535	25134.45183	0.99109	0.98788
Toluene	8.184	4626.47	1414.78	5.79	20.33705	139942.22937	1.01644	1.01356
DMSO diluent	11.488	25536.43	3520.00	31.96	22.69509	50908.16061	0.64382	0.63954

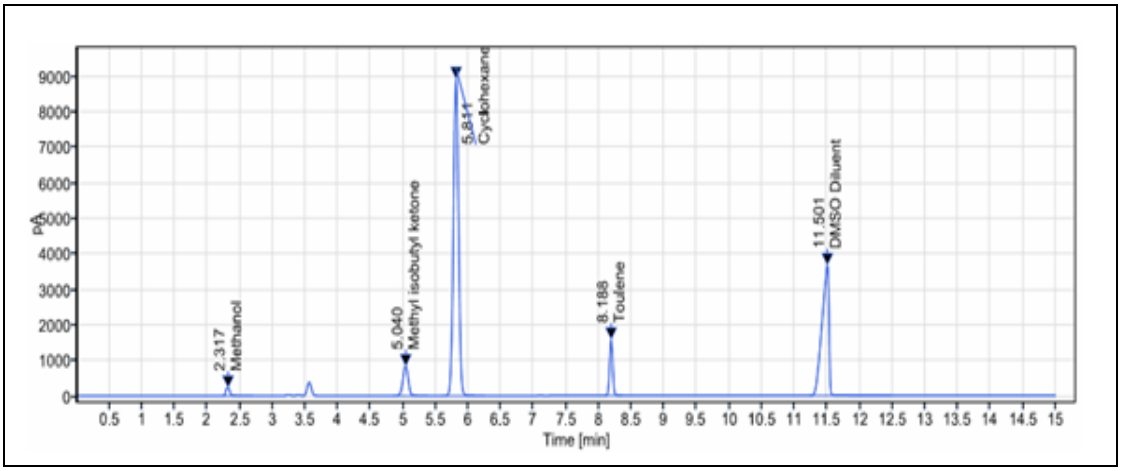
FIG. 9: CHROMATOGRAM OF SPIKED SAMPLE SOLUTION

TABLE 4: SPECIFICITY DATA OF RESIDUAL SOLVENTS

Solvent name	Individual retention time	Spiked retention time
Methanol	2.313	2.314
Methyl isobutyl ketone	5.033	5.033
Cyclohexane	5.804	5.805
Toulene	8.184	8.184

System Suitability: System suitability was carried out by injecting 6 injections. %RSD responses of each solvent were found to be less than 15%. Hence the system is suitable to carry out the analysis for the estimation of residual solvents in Luliconazole.

The chromatogram of system suitability is mentioned in **Fig. 10**. The results are mentioned in **Table 5**.



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.317	961.89	222.25	1.11		8160.15910	1.13889	1.02442
Methyl isobutyl ketone	5.040	4721.07	826.79	5.44	21.34583	17457.53846	0.96379	0.95473
Cyclohexane	5.811	48614.08	8920.64	56.01	5.15957	25269.75006	0.98793	0.98301
Toluene	8.188	5163.26	1571.05	5.95	20.30403	138846.30019	1.02560	1.02427
DMSO diluent	11.501	27334.64	3665.16	31.49	22.31645	48425.91431	0.63817	0.63404

FIG. 10: CHROMATOGRAM OF SYSTEM SUITABILITY

TABLE 5: DATA OF SYSTEM SUITABILITY FOR RESIDUAL SOLVENTS

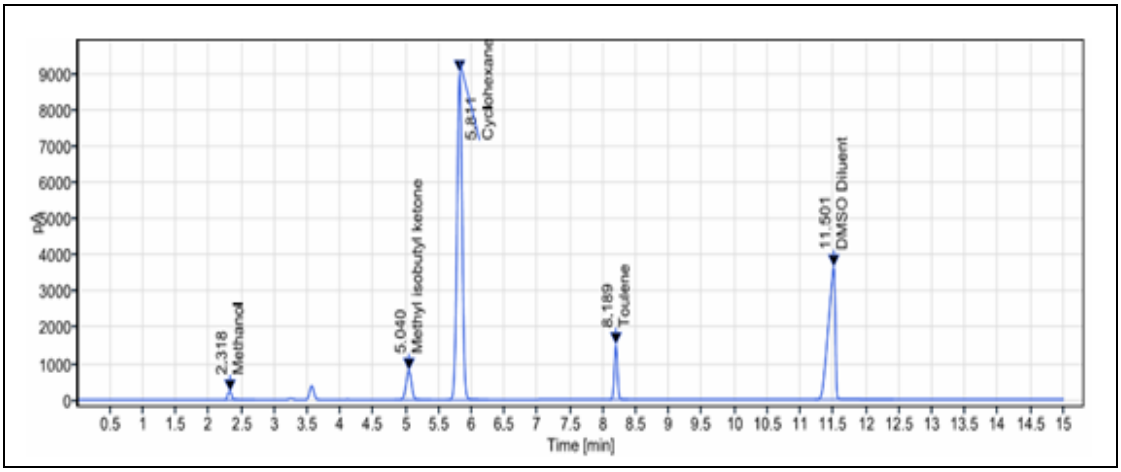
Solvent Name	Methanol		Methyl isobutyl ketone		Cyclohexane		Toulene	
S. no.	Rt	Area	Rt	Area	Rt	Area	Rt	Area
1	2.32	1016.93	5.044	5143.22	5.814	54941.480	8.190	5580.940
2	2.318	910.05	5.040	4561.43	5.811	49365.290	8.189	4918.150
3	2.317	961.89	5.040	4721.07	5.811	48614.080	8.188	5163.260
4	2.316	977.64	5.038	4817.60	5.810	50130.360	8.188	5210.900
5	2.316	938.12	5.039	4590.56	5.809	48183.130	8.187	4944.670
6	2.316	1017.17	5.039	4975.44	5.809	50257.040	8.187	5448.210
Avg	2.3172	970.30	5.040	4801.55	5.811	50248.563	8.1882	5211.022
SD	0.0016	42.81	0.002	226.22	0.002	2439.477	0.0012	265.366
%RSD	0.07	4.41	0.04	4.7	0.032	4.8	0.01	5.09

Precision:

Method Precision: The Method precision was checked, and the % RSD was found to be 4.41 for Methanol, 4.71 for Methyl isobutyl ketone, 4.85 for Cyclohexane and 5.09 for Toulene were within limits. The % RSD for precision was also found to be NMT 15%. The chromatogram of method precision is mentioned in **Fig. 11**. It indicates that the method was precise, and the results are mentioned in **Table 6**.

TABLE 6: METHOD PRECISION DATA FOR RESIDUAL SOLVENTS

System suitability parameters	Observed value				Acceptance Criteria
	Methanol	Methyl isobutyl ketone	Cyclohexane	Toluene	
Tailing factor	1.1	0.9	0.9	1.0	NMT 2.0
%RSD of Retention time	0.07	0.04	0.032	0.01	NMT 1.0
%RSD of Peak responses	4.41	4.71	4.85	5.09	NMT 15.0
% Content of all residual solvents	104.3	100.3	101.2	102.4	90.0 to 125.0
%RSD of % content of all residual solvents	2.4	1.4	2.7	2.5	NMT 5.0



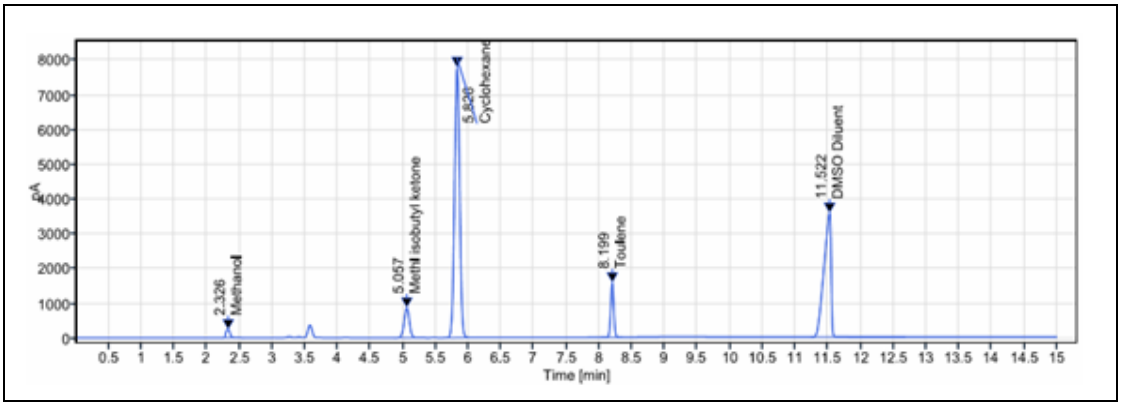
Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.318	910.05	209.50	1.05		8101.11171	1.12204	1.00823
Methyl isobutyl ketone	5.040	4561.43	797.19	5.25	21.28175	17420.05182	0.97273	0.96409
Cyclohexane	5.811	49365.29	9029.25	56.84	5.15622	25259.42239	0.99510	0.99209
Toluene	8.189	4918.15	1502.49	5.66	20.32539	139489.86501	1.01647	1.01330
DMSO diluent	11.501	27094.31	3651.60	31.20	22.23403	47865.76686	0.63875	0.63456

FIG. 11: CHROMATOGRAM OF METHOD PRECISION

Intermediate Precision: The Intermediate precision was checked, and the % RSD was found to be 1.2 for methanol, 1.4 for methyl isobutyl ketone, 1.5 for cyclohexane, and 0.9 for toluene were within limits. It indicates that the method was precise, and the results are mentioned in **Table 7**. The chromatograms of intermediate precision are mentioned in **Fig. 12.**

TABLE 7: INTERMEDIATE PRECISION DATA FOR RESIDUAL SOLVENTS

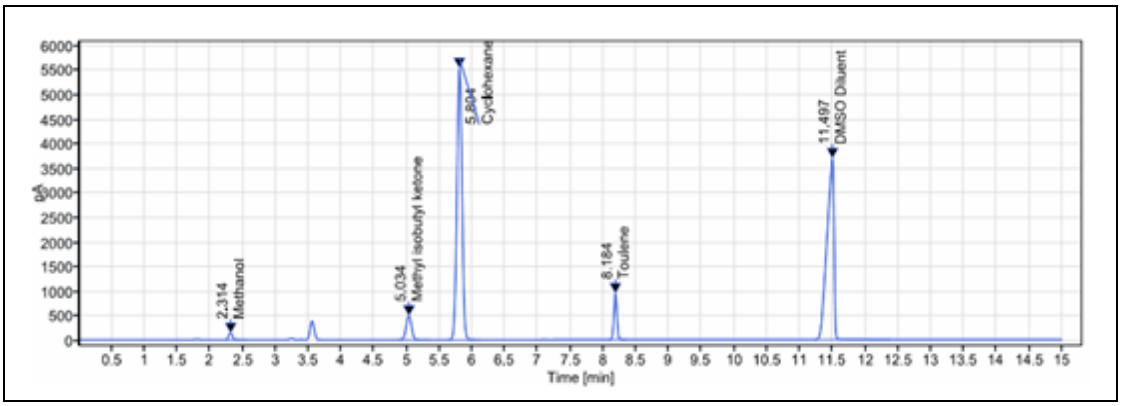
System suitability parameters	Observed value				Acceptance Criteria
	Methanol	Methyl isobutyl ketone	Cyclohexane	Toluene	
Tailing factor	1.1	0.9	0.9	1.0	NMT 2.0
%RSD of Retention time	0.03	0.03	0.03	0.02	NMT 1.0
%RSD of Peak responses	4.47	4.07	4.84	4.3	NMT 15.0
% content of all residual solvents	97.9	100.4	100.0	99.8	90.0 to 125.0
%RSD of % content of all residual solvents	4.5	1.8	2.8	2.4	NMT 5.0



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.326	994.23	229.04	1.24		81.55.84522	1.11144	1.00885
Methyl isobutyl ketone	5.057	4741.02	855.16	5.89	21.72146	18586.21646	0.98549	0.97916
Cyclohexane	5.826	42309.85	7777.56	52.60	5.22243	25526.47287	1.00482	1.00338
Toluene	8.199	5137.13	1566.89	6.39	20.32787	140008.63966	1.01682	1.01263
DMSO diluent	11.522	27248.11	3567.88	33.88	22.01360	46262.74702	0.62651	0.62235

FIG. 12: CHROMATOGRAM OF INTERMEDIATE PRECISION

Accuracy: The average recoveries of the Methanol, Methyl isobutyl ketone, cyclohexane, and toluene were 107.3%, 110.9%, 102.5%, and 107%, percentage RSD was less than 15%, which indicate that the method was accurate and the results are mentioned in **Table 8**. The chromatogram of accuracy is mentioned in **Fig. 13**.



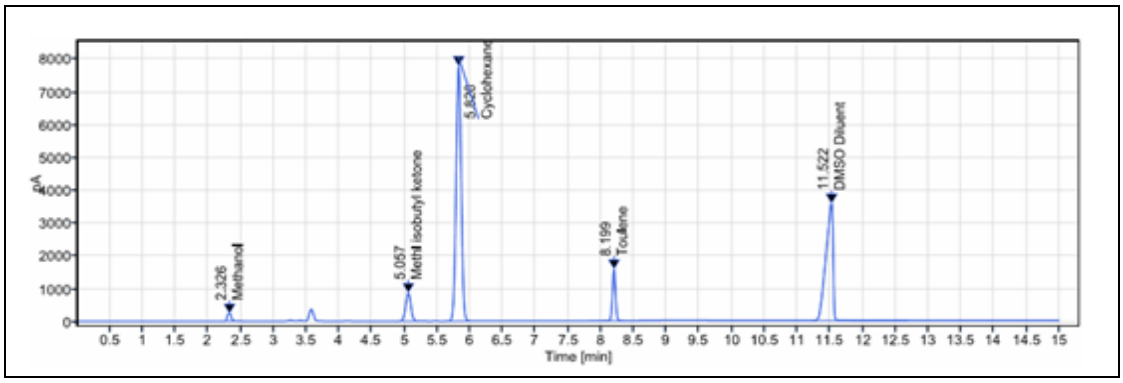
Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.314	561.23	130.65	0.87		8179.65610	1.14141	1.02834
Methyl isobutyl ketone	5.034	2794.85	484.67	4.35	21.22769	17115.38062	0.96659	0.95775
Cyclohexane	5.804	30042.18	5534.42	46.79	5.13100	25316.91007	1.01676	1.01659
Toluene	8.184	3041.90	937.93	4.74	20.46914	142456.85753	1.02637	1.02250
DMSO diluent	11.497	27762.57	3683.34	43.24	21.96116	45777.45342	0.63591	0.63197

FIG. 13: CHROMATOGRAM OF ACCURACY

TABLE 8: ACCURACY DATA FOR RESIDUAL SOLVENTS

Parameters	Observed value				Acceptance Criteria
	Methanol	Methyl isobutyl ketone	Cyclohexane	Toluene	
Tailing factor	1.1	0.9	0.9	1.0	NMT 2.0
% Recovery of all residual solvents	103.08	101.5	104.5	108.1	90.0 to 110.0
%RSD of % recovery of all residual solvents	4.1	4.2	3.2	4.4	NMT 5.0

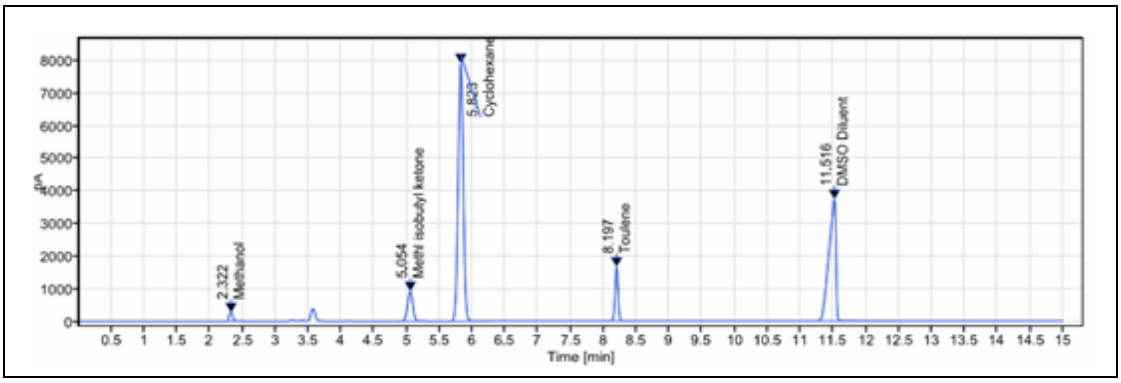
Robustness: The robustness of the method was checked by changing flow rate and was found that the parameters were within limits; the %RSD was found to be less than 2%; hence the method is robust. The chromatogram of robustness is mentioned in **Fig. 14.**



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.326	994.23	229.04	1.24		8155.84522	1.11144	1.00885
Methyl isobutyl ketone	5.057	4741.02	855.16	5.89	21.72146	18586.21646	0.98549	0.97916
Cyclohexane	5.826	42309.85	7777.56	52.60	5.22243	25526.47287	1.00482	1.00338
Toluene	8.199	5137.13	1566.89	6.39	20.32787	140008.63966	1.01682	1.01263
DMSO diluent	11.522	27248.11	3567.88	33.88	22.01360	46262.747002	0.62651	0.62235

FIG. 14: CHROMATOGRAM OF ROBUSTNESS

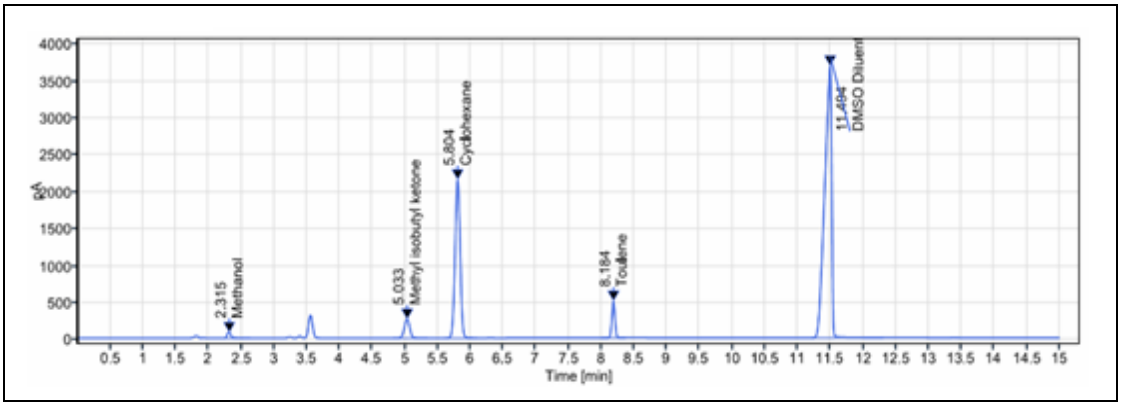
Ruggedness: The ruggedness of the method was checked by observing by the different analysts, and the result was found to be in the specified limits; the % RSD was found to be less than 2%. The chromatogram of ruggedness is mentioned in **Fig. 15**.



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.322	1045.09	250.11	1.27		8959.36167	1.12667	1.02219
Methyl isobutyl ketone	5.054	4973.24	901.97	6.04	22.21837	18736.52505	0.97732	0.96989
Cyclohexane	5.823	42795.71	7886.58	51.98	5.26204	25914.99148	0.99877	0.99737
Toluene	8.197	5398.11	1652.31	6.54	20.48424	141602.47604	1.01421	1.01075
DMSO diluent	11.516	28125.42	3723.54	34.16	22.34056	48080.62895	0.62863	0.62448

FIG. 15: CHROMATOGRAM OF RUGGEDNESS

LOD and LOQ: The detection limit was found to be 0.003 for Methanol, 0.0007 for methyl isobutyl ketone, 0.005 for cyclohexane, and 0.16 for toluene. The quantification limit was found to be 0.0009 for methanol, 0.002 for Methyl isobutyl ketone, 0.001 for cyclohexane, and 0.51 for toluene. The chromatogram of LOD and LOQ is mentioned in **Fig: 16**.



Compound name	Peak retention time	Area	Height	Area%	Peak resolution USP	Peak theoretical plates USP	Peak tail factor	Peak asymmetry 10 perc
Methanol	2.315	305.85	73.37	0.72		8767.76030	1.12791	1.01687
Methyl isobutyl ketone	5.033	1454.49	254.36	3.44	21.65770	17525.84154	0.97606	0.96807
Cyclohexane	5.804	11575.97	2140.52	27.42	5.18064	25444.54111	1.00023	0.99704
Toluene	8.184	1617.07	495.13	3.83	20.45568	140767.56361	1.00620	1.00136
DMSO diluent	11.494	27269.27	3677.40	64.58	22.36406	48505.73054	0.63750	0.63355

FIG. 16: CHROMATOGRAM OF LOD AND LOQ

CONCLUSION: From the above experimental results and parameters it was concluded that this newly developed method for the estimation of residual solvents of methanol, cyclohexane, methyl isobutyl ketone and toluene in Lulucinazole API was found to be simple, precise, accurate, specific, robust, rugged and high resolution and shorter retention time makes this method more acceptable and cost-effective, and it can be effectively applied for routine analysis in research institutions, quality control department in industries, approved testing laboratories, bio-pharmaceutical and bio-equivalence studies and in clinical pharmacokinetic studies in the near future.

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