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DEVELOPMENT AND VALIDATION OF THE HS-GC-FID METHOD FOR THE QUANTIFICATION OF RESIDUAL SOLVENTS IN DESLORATADINE

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ABSTRACT

Testing for residual solvents is a crucial component of both reference material certification and pharmaceutical quality control. Developing and validating a head space-gas chromatography method for measuring residual solvents in desloratadine in pharmaceutical dosage forms was the aim of the current investigation. To create desloratadine, an active ingredient in pharmaceuticals, the pharmaceutical industry commonly uses organic solvents such as methanol, diethyl ether, dichloromethane, and tetrahydrofuran. A novel technique for measuring residual solvents in desloratadine was created using a flame ionization detector and headspace gas chromatography. HP1 Column (30m×0.53mm, 1.8µm), intake port maintained at 250°C, detector temperature 260°C, oven temperature 190°C, and injection volume 1µl with 1:50 split ratio utilizing nitrogen as a carrier gas at a flow rate of 1ml/min were the optimum chromatographic conditions. Using criteria from the International Conference on Harmonization, the method's linearity, range, detection limit, quantitation limit, accuracy, precision, specificity, system appropriateness, and robustness were all validated. It was determined that the idea was appropriate for determining four distinct residual solvents. The approach is particular, linear, exact, accurate, and sensitive, according to validation data, where recoveries varied from 90 to 110 percent. This thoroughly tested technique has been used to identify any remaining solvents in actual desloratadine bulk samples.

Keywords: Desloratadine, Gas Chromatography, ICH Guidelines, Method Development, Validation, Residual Solvents.

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INTRODUCTION

The organic solvents used during the production of excipients, active pharmaceutical ingredients (APIs), and drug products but not eliminated are referred to as residual solvents in medicines. There are numerous stages in the synthetic approach when solvents are used. Some important aspects influencing the amount of residual solvents in final products are the drying conditions of products, the interaction of residual solvents with similar polarity, and the purification techniques of intermediates.[1] The choice of organic solvents is critical because they affect crystal shape, particle size, and dissolving characteristics in addition to being essential for the reaction rate and yield of APIs.[2] Internationally acknowledged rules for the determination of residual solvents have been published by the International Conference on Harmonization (ICH). Comprehensive guidelines have been provided for residual solvents in drug substances, excipients, and drug products, by ICH Q3C.[1] When it comes to detecting and analyzing residual solvents, which are mostly volatile organic compounds, gas chromatography (GC) is the most significant tool because of its benefits in exceptional sensitivity, differentiated selectivity, high efficiency, and fast analysis cycle.[3,4,5] Long-acting, non-sedative desloratadine (DLT) selectively antagonistically binds to peripheral H1 receptors (Fig.-1). DLT dissolves quite well in methanol and propylene glycol but only very slightly in water.[6] Desloratadine's chemical formula is 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo [5,6] cycloheptane [1,2-b pyridine].[7] According to the literature review, it was found that only a few methods were developed for the estimation of desloratadine in pharmaceutical formulations using LC-MS/MS, HPLC, Spectrophotometric method, Spectrofluorimetric technique, UPLC, Ion pair chromatography, Electrophoresis, and TLC

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method.[8-21] Most of the methods discussed were created for biological sample analysis and need time-consuming sample preparation procedures. This produces a lot of solvent waste, which needs to be disposed of expensively and could harm the environment. In addition, the authors were motivated to develop a quick, simple, economical, and eco-friendly GC method due to the absence of a well-established pharmacopoeial method for DLT estimates. As per the ICH requirements, the current work details the validation of a GC method for DLT detection in the presence of residual solvents.[22] The created technique is used to regularly examine DLT in the dose form of medicinal tablets.

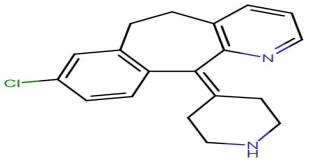

Fig.-1: Desloratadine Chemical Structure

EXPERIMENTAL

Material and Methods

Chemicals and Reagents

Chandra Labs, Hyderabad, provides a complimentary sample of desloratadine. Methanol from Qualigens that meets HPLC standards. Qualigens provided the dimethyl sulfoxide, while Sigma Aldrich provided the dichloromethane, diethyl ether, and tetrahydrofuran.

Instrument and Chromatographic Conditions

Nitrogen was used as the carrier gas for the analysis, which was carried out on an Agilent gas chromatography model 7697A headspace sampler with an HP1 column and FID detector. Tables-1 and 2 list the chromatographic and headspace conditions.

Table-1: Conditions for Chromatography

Column	Column HP1, (30m×0.53mm)1.8µm
Oven's temperature	190°C
First hold duration	Five minutes
Mobile phase	N_2
Flow	1ml/min
Runtime	21min
Injector's temperature	250°Centigrade
Detector's temperature	260°Centigrade

Table-2: Headspace

Loop's temp.	110°Centigrade
Oven's temp.	100°Centigrade
Temp. of the transfer line	125°Centigrade
Cycle time of GC	30minutes
Equilibration period of Vial	5minutes

Preparation of Solutions

Standard Stock-I Preparation

In a 250 ml volumetric flask filled with diluent DMSO, precisely weigh 500 mg methanol, 500 mg diethyl ether, 500 mg dichloromethane, and 500 mg tetrahydrofuran. Shake thoroughly.

Standard Stock-II Preparation

In a 200 ml volumetric flask, pipette off 10 ml of the solution above, then add diluent to make up the remaining volume. In a headspace vial, pipette one milliliter of the previously prepared solution, and then close the vial with a crimper.

Test Sample Preparation

500 mg of the test sample (desloratadine API) should be carefully weighed, put into a 50 mL volumetric flask, and vortexed for five minutes after adding a certain amount of diluent. Next, use diluent to make up

the volume and thoroughly mix. One milliliter of the previously made solution should be pipetted into the headspace vial. The vial should then be sealed with a crimper.

Procedure

The prepared solutions are transferred into 5 ml headspace vials and sealed using a crimper. Headspace analysis is performed on the prepared standard and sample solutions.

Analytical Method Development

The development and simultaneous measurement of residual solvents in desloratadine are done through several trials. Ultimately, improved resolution and appropriate peak shape discussed in Fig.-2 led to an improved separation.

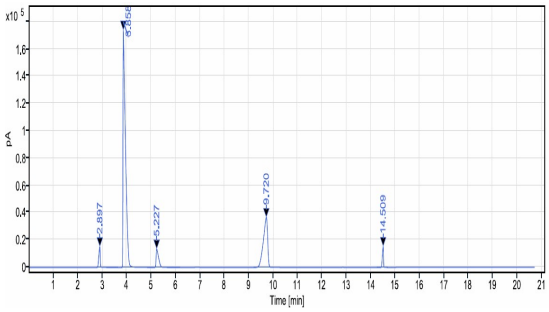

Fig.-2: Optimized Chromatogram of Residual Solvents

RESULTS AND DISCUSSION

Method Development

Method development involved several experiments utilizing different diluents, adjusting chromatographic settings, and taking into account the physicochemical characteristics of the analyte, which was optimized in the last trial by employing DMSO as a diluent. All of the parameters were tuned by injecting the instrument with blank, sample, and standard solution, as shown in the ICH limits. Fig.-2 illustrates the Retention time of blank (DMSO) at 14.509 minutes. The standard retention durations for methanol, diethyl ether, dichloromethane, and tetrahydrofuran were found to be 2.987 min, 3.858 min, and 5.227 min, respectively.

Method Validation

Following ICH criteria, the procedure was validated for various validation parameters.[23]

Linearity

The linearity study of all residual solvents for methanol, diethyl ether, dichloromethane, and tetrahydrofuran ranges from 50 to 150 µg/ml (r2>0.999), and there was good agreement with the amount of solvent calculated using the recommended methodologies. Table-3 provides a summary of the findings. In Fig.-3, 4, 5, and 6, the calibration graphs for each residual solvent are mentioned.

Table-3: Results of Linearity Data of all Residual Solvents

S. No.	Concentration (µg/ml)	Methanol	Diethyl ether	Dichloromethane	Tetrahydrofuran
1	50	266033	560589	20699	91505
2	75	400800	848786	30468	137784
3	100	533095	1121177	41728	188765
4	125	675214	1356789	53147	232164
5	150	833765	1681346	64205	276332

Specificity

Specificity was ascertained by residual solvent non-interference analysis. First, the reagent blank was added to the headspace to record the chromatogram. The standard solution of residual solvents was then introduced to record the chromatogram. Finally, the spiked sample is injected into the chromatograms to record the chromatogram. The chromatograms of the standard solution, the spiked sample solution, and the blank solution are shown in Figs.-7,8,9. The findings of specificity are shown in Table-4.

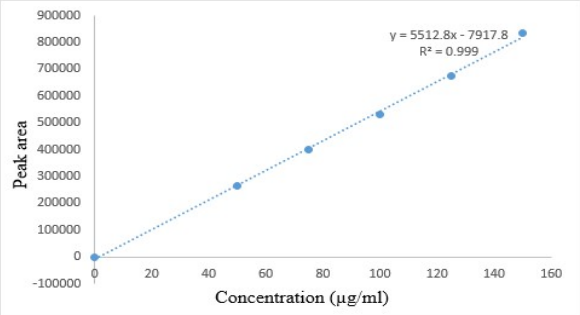

Fig.-3: Linearity Graph of Methanol

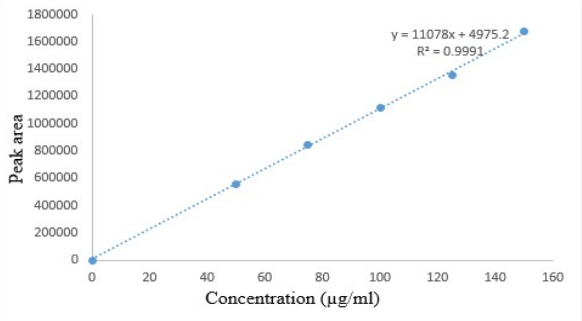

Fig.-4: Linearity Graph of Diethyl Ether

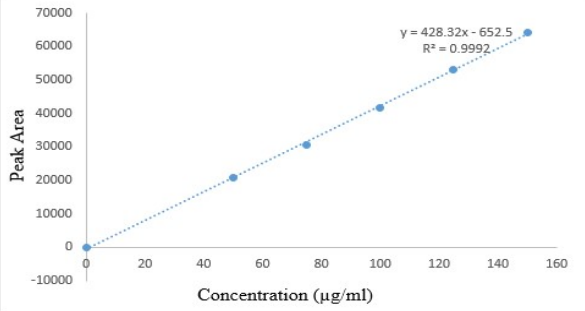

Fig.-5: Linearity Graph of Dichloromethane

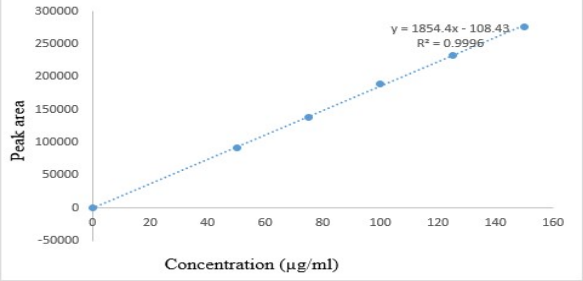

Fig.-6: Linearity Graph of Tetrahydrofuran

Table-4: Residual Solvents Specificity Data

Name of solvent	Individual retention time	Spiked retention time
Methanol	2.897	2.889
Diethyl ether	3.858	3.854
Dichloromethane	5.227	5.218
Tetrahydrofuran	9.720	9.703
DMSO	14.509	14.506

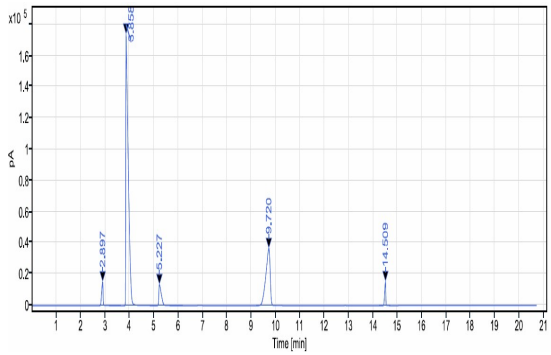

Fig.-7: Standard Solution Chromatogram

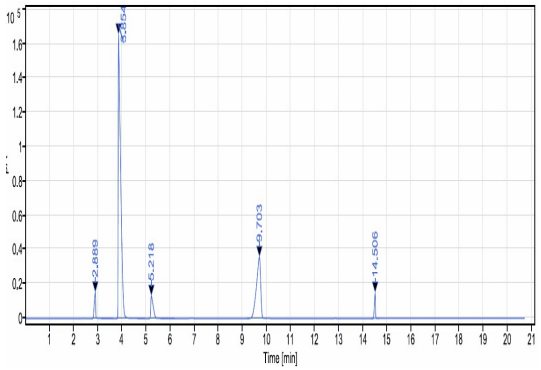

Fig.-8: Sample Solution Chromatogram

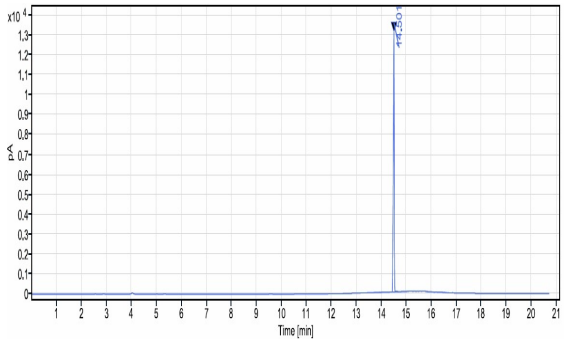

Fig.-9: Blank Solution Chromatogram

System Suitability

To test the suitability of the system, six injections were made. Every solvent's percentage RSD responses were found to be less than 15%. As a result, the system is appropriate for performing the analysis needed to estimate the solvents still present in desloratadine. Table-5 mentions the outcomes.

Table-5: Residual Solvent System Suitability Data

S. No.	Methanol		Diethyl ether		Dichloromethane		Tetrahydrofuran	
	Retention time	Area	Retention time	Area	Retention time	Area	Retention time	Area
1	2.891	60718	3.868	1121177	5.221	94211	9.728	450885
2	2.896	59990	3.855	1128409	5.223	91913	9.719	456116
3	2.895	59336	3.849	1147287	5.221	95481	9.725	456323
4	2.896	60716	3.850	1121137	5.221	94204	9.721	451646
5	2.897	60005	3.855	1142514	5.224	94251	9.727	451251
6	2.891	62121	3.857	1125139	5.221	94533	9.719	451332
Average	2.894	60481	3.856	1130944	5.222	94099	9.723	452926
SD*	0.0026	957.04	0.0068	11248.6	0.0013	1176.7	0.0040	2563.8
%RSD	0.092	1.582	0.176	0.995	0.025	1.251	0.041	0.566

SD= Standard deviation

Precision

When the method's precision was examined, the percentage RSD was discovered to be within acceptable criteria for methanol, diethyl ether, dichloromethane, and tetrahydrofuran, at 2.53, 1.03, 0.92, and 1.29, respectively. It was also discovered that the precision % RSD was not more than (NMT) 5%. Fig.-10 mentions the method of precision chromatogram. It suggests that the procedure was precise, and Table-6 lists the outcomes.

Table-6: Residual Solvents Method Precision Data

Sample No.	Methanol	Diethyl ether	Dichloromethane	Tetrahydrofuran
1	100.2	97.5	99.4	102.3
2	96.5	98.6	97.6	99.6
3	94.6	98.6	97.1	99.4
4	97.5	100.2	98.6	101.3
5	101.4	98.5	97.4	102.5
6	97.5	97.4	97.3	101.1
Average	97.9	98.5	97.9	101.0
SD*	2.477	1.011	0.903	1.307
%RSD	2.53	1.03	0.92	1.29

SD= Standard deviation

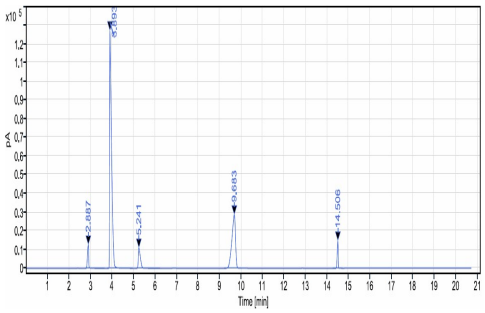

Fig.-10: Method Precision Chromatogram

Accuracy

The findings are shown in Table-7 and show that the procedure was accurate. The average recoveries of the methanol, diethyl ether, dichloromethane, and tetrahydrofuran were 107.3%, 110.9%, 102.5%, and 107%, respectively. The percentage RSD was less than 15%. Figs.-11a, b, and c mention the accuracy of chromatograms.

Table-7: Accuracy Data for Residual Solvents

Level	Methanol	Diethyl ether	Dichloromethane	Tetrahydrofuran	Acceptance criteria
50%	102.5	99.5	101.5	99.8	% Recovery of all residual solvents should be within 90.0 to 110.0 %
100%	100.1	100.1	101.9	99.4	
150%	98.7	101.2	102.2	98.6	

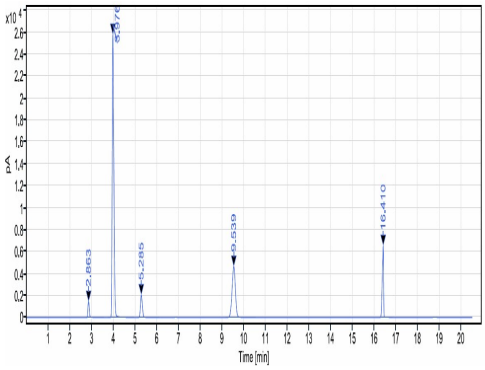

Fig.-11a: Chromatogram for Accuracy 50%

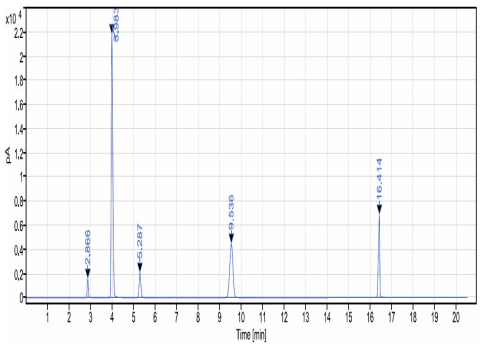

Fig.-11b: Chromatogram for accuracy 100%

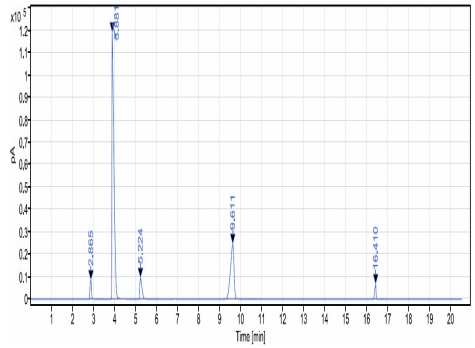

Fig.-11c: Chromatogram for accuracy 150%

LOD and LOQ

The detection limit and quantification limit were calculated for all the residual solvents using standard deviation and slope of the calibration curve values. The results are presented in Table-8.

Table-8: LOD and LOQ Data for Residual Solvents

Parameter	Methanol	Diethyl ether	Dichloromethane	Tetrahydrofuran
LOD	3.12 µg/ml	3.31 µg/ml	4.01 µg/ml	4.01 µg/ml
LOQ	9.50 µg/ml	10.11 µg/ml	12.19 µg/ml	12.38 µg/ml

CONCLUSION

It was discovered that the recently created method for determining the remaining solvents of dichloromethane, methanol, diethyl ether, and tetrahydrofuran in desloratadine API was straightforward, exact, accurate, and specific. Its short retention time also contributed to its increased acceptability and cost-effectiveness. This technique will soon be useful for routine analysis in research facilities, authorized testing facilities, industry quality control departments, biopharmaceutical and bioequivalence investigations, and clinical pharmacokinetic studies.

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CONFLICT OF INTERESTS

There is no conflict of interest, according to the authors.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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