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Research Article

DETERMINATION AND SIMULTANEOUSLY QUANTIFICATION OF FIVE ORGANIC VOLATILE IMPURITIES USING HEAD SPACE GAS CHROMATOGRAPHY IN LEVOCLOPERASTINE FENDIZOATE ACTIVE PHARMACEUTICAL INGREDIENTS AND DOSAGE FORMS

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ABSTRACT

Objectives: Organic chemical solvents are generally used during drug material synthesis, excipients, as well as in the drug product formulation. They are not acceptable in the finished product. Hence, the main objective of our work is development and validation of rapid, sensitive, and selective head space gas chromatography (GC-HS) method for the determination of five organic volatile impurities (OVI) (methanol, ethanol, dichloromethane, toluene, and benzene) in Levocloperastine Fendizoate active pharmaceutical ingredient (API) and commercial syrups.

Methods: The method was developed using a thermal gradient elution program associated with a column having dimensions are ZB-624, 30 m × 0.53 mm × 3.0 µm with a flow rate of 3.0 mL/min and Nitrogen (N2) as a carrier gas. A flame ionization detector was used as a detector, and its temperature is at 250°C whereas the injector temperature is at 225°C. The total run time is 25.0 min.

Results: The newly developed GC-HS method was validated by its specificity and selectivity system precision, and method precision, limit of detection and limit of quantification, linearity, accuracy, robustness, ruggedness, and solution stability as per *International Council for Harmonization* (ICH). Quantization limits for five impurities were 210 ppm for methanol, 350 ppm for ethanol, 42 ppm for dichloromethane, 62 ppm for toluene, and 0.4 ppm for benzene. Correlation coefficient values of linearity were higher than 0.995 for five OVI. The mean recoveries of five impurities were between 90% and 110%.

Conclusion: We found good and accepted results as per ICH guidelines for all validated parameters for five OVI. Thus, the developed GC-HS method was suitable for the separation and quantification of five OVI in Levocloperastine Fendizoate API and commercial syrups at present.

Keywords: Levocloperastine Fendizoate, Organic volatile impurities, Method development and method validation.

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INTRODUCTION

Organic chemical solvents are generally used during drug material synthesis and excipients, as well as in the drug product formulation. They are not acceptable in the finished product, mostly because of their harmfulness, their impact on the consistency of the drug substance's crystals and their taste or odor, which could be uncomfortable for patients. Various processing technologies or procedures are being utilized to eliminate organic chemical solvents. Organic chemical solvents are typically removed under elevated temperature and reduced pressure [1-3]. One of the most complex and challenging analytical activities in the Pharma companies is the detection of residual chemical solvents in medicinal compounds including drug products. The processing of active medicinal ingredients and formulations of pharmaceutical compounds under conditions of good industrial practice requires sufficient quality control of the various ingredients expended in the synthesis. Before any good industrial practice synthesis, organic residual chemical solvents have to be regulated and purity ought to be established. Regulatory guidance reports contain the acceptable amounts of many organic chemical solvents [4,5]. These organic chemical solvents such as methanol, ethanol, dichloro methane, toluene, and benzene were utilized in Levocloperastine Fendizoate synthetic preparation. Levocloperastine Fendizoate (LCF), that is, 1-{2-[(4-chloro-phenyl)-phenylmethoxy]-ethyl}-piperidine [6] is a drug with a central antitussive effect and it is also endowed with an antihistaminic (sharing an ethylamine moiety with H1 receptor antagonists) and papaverine like activity similar to codeine, but without its narcotic effects [7-10]. The structural information of Levocloperastine Fendizoate and five organic volatile impurities (OVI) is shown in Figs. 1 and 2.

Hence, the main objective of our work is development and validation of rapid, sensitive, and selective GC-HS method for the determination of five OVI (methanol, ethanol, dichloromethane, toluene, and benzene) using Flame Ionized detector in Levocloperastine Fendizoate Active pharmaceutical ingredient (API) and Commercial syrups. As per *International Council for Harmonization* (ICH) Q3C (R6), methanol, ethanol were grouped under class-3. Dichloro methane and toluene were grouped under class-2. Benzene was grouped under class-1. Chemical solvents of class-1, 2, and 3 have inherent toxicity to human. Therefore, the organic chemical solvents utilized in Levocloperastine Fendizoate have to be regulated. The quantity level values are considered low level when compared with as 100% specification limit values for opted five chemical solvents. Theses specifications are shown in Table 1.

Literature survey revealed few quantitative techniques like RP-HPLC [11-22], UV spectroscopy [22-25], TLC [26] methods for CPM and RP-HPLC method [27], and UV spectroscopy [28] for LCF are available. Genotoxic impurities in cloperastine fendizoate [27]. So far to our present knowledge, no validated analytical head space gas chromatography (GC-HS) method was available in literature for the determination and quantification of five OVI in Levocloperastine Fendizoate drug and syrup formulation. Therefore, the purpose of this study was to developed and validated a GC-HS methodology for the simultaneous determination of five OVI in Levocloperastine Fendizoate drug and their syrup formulations, which has no literature precedents.

METHODS

Chemicals and reagents

Levocloperastine Fendizoate API was a taken from local well-known laborites. GC grade methanol, ethanol, dichloromethane, toluene,

and benzene and di methyl sulfoxide (DMSO) were purchased from Merck -Mumbai.

Instrumentation
Chromatography was performed on Shimadzu chromatographic system equipped with Shimadzu GC-2010 system with flame ionized detector (FID). Samples were injected through a Teledyne tekmar HT3TM Head space. Data acquisition and integration were performed using GC-solution software.

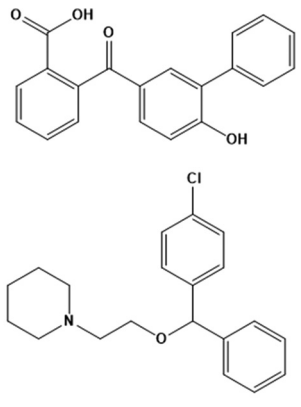
Chromatographic conditions
Column: ZB-624 (30 m, 0.53 mm ID, 3 μm); carrier gas: Nitrogen; flow rate: 3.0 mL/min; injector temperature: 225°C; split ratio: 1:20; oven program: initial 40°C hold for 5 min, increase @ 20°C/min up to 200°C, hold for 12.0 min; detector temperature (FID): 250°C; air gas flow: 400 mL/min; hydrogen gas flow:40 mL/min; total run time is 25 min.

Headspace sampler conditions
Vial temperature: 80°C; needle temperature: 100°C; transfer line temperature: 110°C; vial conditioning time: 30 min; vial pressurize time: 3.0 min; injection volume: 1.0 mL; inject time: 1.0 min; GC cycle time: 40 min.

Table 1: Specifications for five OVI

Name of OVI	ICH specifications (ppm)	In house specifications (ppm)
Methanol	3000	2100
Ethanol	5000	3500
Dichloromethane	600	420
Toluene	890	623
Benzene	2	2

OVI: Organic volatile impurities, ICH: International Council for Harmonization



Chemical Formula: $C_{20}H_{14}O_4$: $C_{20}H_{24}ClNO$
Molecular Weight: 318.33 : 329.87

Fig. 1: Chemical structure of Levocloperastine Fendizoate

Sample and impurity standard preparations

Preparation of benzene stock solution

Weighed and transferred 52.52 mg of Benzene into 100 mL of the volumetric flask containing 70 mL of diluent, shacked well, and diluted to volume with diluent. Further transferred 1.0 mL of the above stock solution into 100 mL of volumetric flask and diluted to volume with diluent.

Standard solution preparation of five OVI's

Weighed and transferred 525.65 mg of methanol, 875.89 mg of ethanol, 106.89 mg of dichloromethane, and 156.85 mg of toluene into 100 mL of the volumetric flask containing 70 mL of diluent, shack well, and diluted to volume with diluent. Further taken 5.0 mL of the above stock solution and 5 mL of benzene stock solution into 50 mL of volumetric flask and diluted to volume with diluent.

The standard headspace vials were prepared with 2 mL of the standard solution and seal the vial with aluminum closure (the standard solution has been prepared with respect to Levocloperastine Fendizoate API concentration).

Preparation of Levocloperastine Fendizoate API sample solution (250 mg/mL)
Accurately weighed about 500.25 mg of Levocloperastine Fendizoate pure API sample into a 10 mL head space vial and add 2.0 mL of diluent and immediately sealed with aluminum closure.

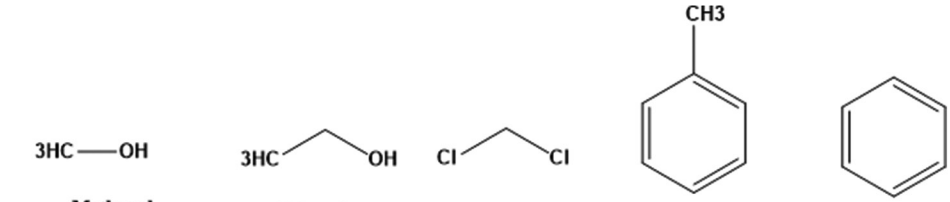
Preparation of Levocloperastine Fendizoate commercial syrup
Weighed and transferred equivalent to 500 mg of Levocloperastine Fendizoate syrup into 10 mL of headspace vial, adds 2 mL of diluent, and immediately sealed with aluminum closure.

Calculation
The organic volatile impurity content was calculated from,

$$\text{ppm}\left(\text{OVI'S}\right)=\frac{\text{Impurity area in LCF API}}{\text{OVI area in Standard solution}}\times\frac{\text{Standard solution concentration}}{\text{Sample solution concentration}}\times 10^6$$

RESULTS

Method development
This method development was implemented following quality-by-design principles including diluent selection and column selection. During the HS-GC method development, to select the most appropriate system parameters to obtain the best separation, sensitivity, and time efficiency, five OVI mixtures were injected under a variety of conditions, for example, at different GC Columns (ZB-Wax: 60 m × 0.32 mm × 1.0 μm, DB-5: 30 m × 0.32 mm × 1.0 μm, ZB-624: 30 m × 0.53 mm × 3.0 μm), HS vial temperature (70–90°C), HS Needle temperature (90–110°C), HS transfer line temperature (90–130°C), GC-FID temperatures (230–280°C), GC Injector temperatures (200–240°C), GC gradients (40–200°C, at the rate of 5–40°C/min), carrier gas flow rates (2.0–5.0 mL/min), different diluents (NMP, DMSO, and DMF), etc. The final HS-GC conditions used for method



Methanol
Chemical Formula: CH_4O
Molecular Weight: 32.04

Ethanol
C_2H_6O
46.07

Dichloromethane
CH_2Cl_2
84.93

Toluene
C_7H_8
92.14

Benzene
C_6H_6
78.11

Fig. 2: Chemical structures of five organic volatile impurities

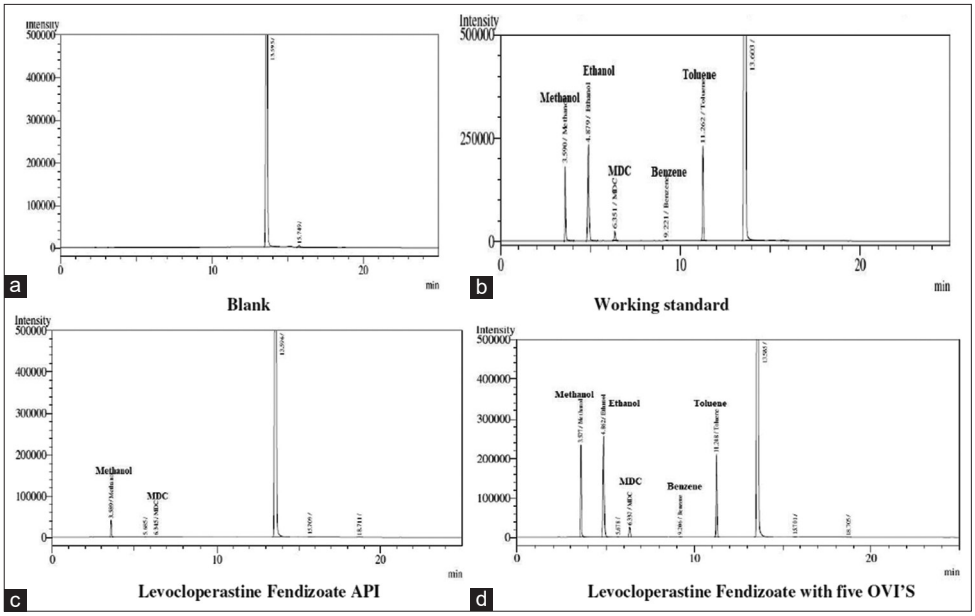


Fig. 3: (a) Blank chromatogram (DMSO), (b) Standard mixed organic volatile impurities solution, (c) Levocloperastine Fendizoate active pharmaceutical ingredient (d) Spiked solution

Table 2: Specificity data for five OVI

S. No.	Name of OVI'S	RT (min)	Theoretical plates	Tailing factor	USP resolution
1	Methanol	3.59	30272	1.29	0.00
2	Ethanol	4.88	20319	1.17	11.90
3	MDC	6.35	43626	1.04	11.50
4	Toluene	11.26	202205	1.02	20.55
5	Benzene	9.22	102677	1.1	25.89

OVI: Organic volatile impurities

Table 3: System precision data for five OVI'S

No. of Injections	Methanol	Ethanol	MDC	Toluene	Benzene
1	592746	1249429	108925	753064	3410
2	602954	1318948	110691	790372	3442
3	567741	1231387	110046	774459	3251
4	586966	1262978	109983	773417	3418
5	577167	1276221	108628	768245	3336
6	607239	1342436	108168	769965	3458
ACVG	589136	1280233	109407	771587	3386
STDV	15082	42466	976	12011	78
% RSD	2.56	3.32	0.89	1.56	2.31

OVI: Organic volatile impurities

Table 4: Method precision data for five OVI'S

No. of Preparations	Methanol	Ethanol	MDC	Toluene	Benzene
1	598547	1214245	108316	850094	3485
2	604917	1227141	108363	850759	3591
3	582908	1171082	107579	838939	3469
4	614479	1260170	106970	829886	3274
5	602114	1221165	107701	840843	3300
6	589781	1189699	106311	828840	3256
ACVG	598791	1213917	107540	839894	3396
STDV	11209	30946	793	9447	138
% RSD	1.87	2.55	0.74	1.12	4.06

OVI: Organic volatile impurities

Table 5: LOD and LOQ data for five OVI'S

OVI'S	LOD Con. (ppm)	LOQ Con. (ppm)	LOD area (n=3)	LOQ area (n=6)
Methanol	64	210	9933	30405
Ethanol	106	350	7974	25018
MDC	13	42	11078	29677
Toluene	19	62	11637	31588
Benzene	0.1	0.4	320	671

LOD: Limit of detection, LOQ: Limit of quantification, OVI: Organic volatile impurities

validation were obtained based on optimized HS and GC parameters. Each of the solvents was injected once separately to determine method specificity and signal response sensitivity.

Method validation

The developed GC-HS method was validated as per ICH guidelines [29]. The method was validated for specificity and selectivity system precision, and method precision, limit of detection (LOD), and limit of quantification (LOQ), linearity, accuracy, robustness, ruggedness, and solution stability.

Specificity and selectivity

The selectivity of this procedure was checked to make sure the Levocloperastine Fendizoate and diluent (DMSO) did not interfere with analysis of five OVI. Levocloperastine Fendizoate drug sample, working standard solvent solution, solution of Levocloperastine Fendizoate spiked with opted five OVI (spiked concentration was same as standard solvent solution) and diluent (DMSO) blank were prepared and analyzed by way of suggested gas chromatographic method. The characteristic chromatograms for selectivity are shown in Fig. 3. Chromatograms exhibit that the retention times of five OVI, namely, methanol, ethanol, dichloromethane, toluene, and benzene are completely different. This also proved that Levocloperastine Fendizoate drug has no effect on analysis of opted five OVI. By comparison, blank peak did not overlap peaks of opted five OVI. The resolution among the opted five OVI was too acceptable (≥10). Hence, it's highly selective method. The corresponding data are shown in Table 2.

System precision

System precision was established by six measurements of the standard solution at the 100% concentration levels on the same day. Six

Table 6: Linearity data for five OVI

Con. (%)	Methanol Avg. area (n=2)	Ethanol Avg. area (n=2)	MDC Avg. area (n=2)	Toluene Avg. area (n=2)	Benzene Avg. area (n=2)
*LOQ	30756	26105	23012	31948	680
25	143533	300313	27805	202035	863
50	278253	594547	54714	402835	1709
75	411185	885312	82959	615261	2510
100	563679	1234429	110710	833638	3294
150	865358	1933873	167225	1278052	5002
Correlation (r2)	0.999	0.999	0.997	1.000	1.000

*LOQ=Methanol-10%, Ethanol-10%, MDC-10%, Toluene-10% and Benzene-20%. OVI: Organic volatile impurities

Table 7: LOQ precision data for five OVI'S

No. of Injections	Methanol area	Ethanol area	MDC area	Toluene area	Benzene area
1	28984	23641	25450	31209	652
2	29177	23496	25482	31109	685
3	31593	26815	26569	31931	675
4	31183	25913	24497	31518	689
5	30937	25722	25837	31818	658
6	30555	24521	26227	31941	665
ACVG	30405	25018	25677	31588	671
STDV	1082	1341	722	367	15
% RSD	3.56	5.36	2.81	1.16	2.21

OVI: Organic volatile impurities, LOQ: Limit of quantification

Table 8: Accuracy data for five OVI'S

Name of OVI'S	Recovery at 50% (%)	Recovery at 100% (%)	Recovery at 150% (%)	Recovery at LOQ% (%)
Methanol	100.45	101.74	101.54	104.98
Ethanol	98.66	99.73	101.16	103.43
MDC	98.18	101.09	101.92	104.35
Toluene	96.94	100.27	102.12	101.54
Benzene	106.69	101.84	99.50	101.59

OVI: Organic volatile impurities, LOQ: Limit of quantification

Table 9: Robustness data for five OVI'S

Name of OVI'S	Flow rate (mL/min)		Vial Cond. Temperature (°C)	
	2.8 mL/min (%RSD)	3.2 mL/min (%RSD)	75°C (%RSD)	85°C (%RSD)
Methanol	2.95	2.94	5.61	2.9
Ethanol	3.45	3.88	6.4	3.9
MDC	1.59	0.69	2.7	1.59
Toluene	1.89	0.97	4.14	2.15
Benzene	1.57	0.74	1.74	2.55

OVI: Organic volatile impurities

injections of standard OVI solution were injected into the GC-HS system to evaluate the system precision of developed method. The relative standard deviation (RSD) was calculated for each OVI. The obtained %RSD of each impurity is not more than 10%. The corresponding data are shown in Table 3.

Method precision

The gas chromatographic method precision was verified by analyzing the Levocloperastine Fendizoate drug sample spiked with opted five OVI's different solvents at 100% specification limit values. The method precision was vented as mean concentration quantified and relative standard deviation of six quantified values of five opted OVI'S. The relative standard deviation calculated for opted five OVI'S was noticed as ≤10%, which proved that gas chromatographic method was precise

Table 10: Ruggedness data for five OVI'S

Different days by different analysts	% RSD				
	Methanol	Ethanol	MDC	Toluene	Benzene
Day-1					
Analyst-1	4.95	6.49	1.85	2.44	1.3
Analyst-2	3.34	4.76	1.41	2.19	2
Analyst-1 and 2	4.12	5.67	1.71	4.91	2.24
Day-2					
Analyst-1	3.58	4.17	0.97	1.77	1.83
Analyst-2	4.69	3.27	0.78	0.81	1.67
Analyst-1 and 2	3.98	3.93	1.16	4.31	1.86
Analyst-1					
Day-1 and 2	4.70	5.27	1.48	2.35	1.54
Analyst-2					
Day-1 and 2	4.08	3.98	1.13	1.81	2.03

Table 11: Solution stability data for five OVI'S

Name of OVI	Variation of Solution stability (%)		
	After 12 h	After 24 h	After 48 h
Methanol	2.49	4.02	3.25
Ethanol	1.17	2.04	2.89
MDC	2.96	3.40	3.53
Toluene	1.01	2.25	1.60
Benzene	2.22	3.17	3.51

OVI: Organic volatile impurities

for evaluation of opted five OVI'S in Levocloperastine Fendizoate drug. The corresponding data are shown in Table 4.

LOD and LOQ

It is of great importance to find out the minimum amount of analyte, which can be detected as well as quantify with accuracy and reproducibility. For this LOD and LOQ were determined by using signal-to-noise(s/n) ratio of 3:1 and 10:1. Hence, 3:1 is stands for LOD 10:1 is stands for LOQ. The quantification and detection limits with data and chromatograms for five OVI'S are shown in Figure 4 and Table 5.

Linearity and range

Analytical method linearity is defined as the ability of the method to obtain test results that are directly proportional to the analyte concentration, within a specific range. The mean peak area obtained from the GC-HS was plotted against corresponding concentrations to obtain the calibration graph. The results of linearity study gave linear relationship over the concentration range of LOQ to 150% for five OVI. The correlation (r2) was found to be not <0.995, indicating a linear relationship between the concentration of analyte and area under the peak. All values and linearity graphs for five OVI'S are shown in Table 6.

Precision at LOQ

The quantification limit values for opted five solvents were confirmed by precision examination. The determined percent relative standard

Table 12: Five OVI'S content in marketed formulation

Name of Formulation	Label claim (mg)	Methanol (ppm)	Ethanol (ppm)	MDC (ppm)	Toluene (ppm)	Benzene (ppm)
Levocloperastine Fendizoate (Esticof-LVP)	35.4	Bellow LOQ	Not detected	Not detected	Not detected	Not detected
Levocloperastine Fendizoate (Drycotus)	35.4	Bellow LOQ	Not detected	Not detected	Not detected	Not detected

OVI: Organic volatile impurities

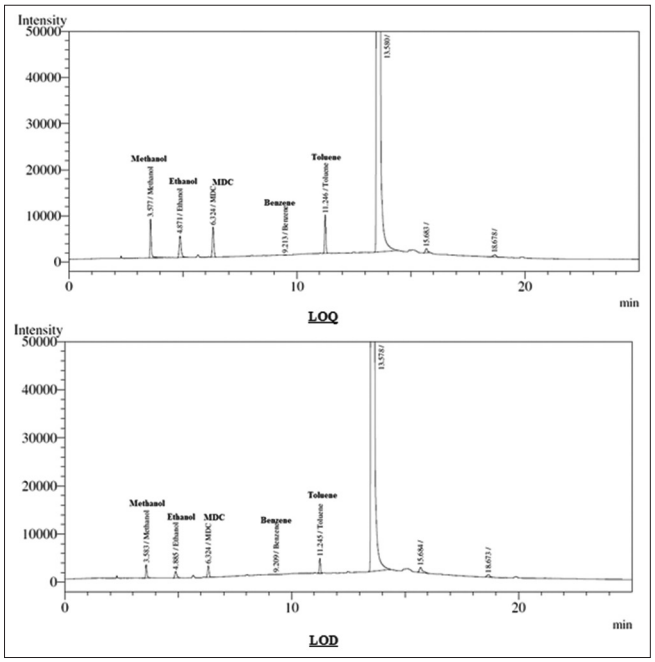


Fig. 4: Typical limit of quantification and limit of detection Chromatograms for five active pharmaceutical ingredient's

deviation of six area responses of opted five OVI'S at their quantification limit level. The relative standard deviation was noticed as ≤10%. This confirmed the quantification limit levels for opted five OVI. The corresponding data are summarized in Table 7.

Accuracy

Appropriate amounts of opted five OVI'S were spiked to Levocloperastine Fendizoate drug sample with replicates (n=3) at LOQ level, 50% level, 100% level, and 150% level of specification quantity value. Theses spiked samples were analyzed by way of suggested gas chromatographic method and ascertained the recoveries of opted five OVI'S at every level. The ascertained values of recoveries of opted five solvents for the suggested gas chromatographic method used were in the range 90-110%, which proved that the gas chromatographic method is accurate enough for evaluation of five OVI'S in Levocloperastine Fendizoate drug sample. The obtained results are shown in Table 8.

Robustness

It assists to find out the effect of slight variations in the different chromatographic conditions. Robustness of the method was checked by varying the flow rate (±0.2 with 3.0 mL/min) and vial condition temperature (±5°C with 80°C). The standard five OVI solutions were injected under each condition. The results were estimated for the mean and standard deviation and % RSD is not more than 10%. The data are shown in Table 9.

Ruggedness

Ruggedness of the method was evaluated by performing the sample analysis in six replicates using different analyst on different days and the results were obtained within the acceptance criteria indicating that the method is rugged within the specified range. The %RSD was calculated for day wise and analyst wise as well as individual and cumulative for five OVI'S. The obtained RSD is not more than 10.0%. The results are presented in Table 10.

Solution stability

The five OVI 100% specification level standard solution is spiked with Levocloperastine Fendizoate API sample in Dimethyl sulfoxide as a diluent. Hence, we have to check whether these spiked solution is stable or not. Hence, we have prepare the five OVI's standard solution in Levocloperastine Fendizoate sample for four time intervals (initial hours, after 12 h, after 24 h, and after 48 h) on the 1st day and kept at room temperature. Then, these solutions are injected two times at initial hours, after 12 h, after 24 h, and after 48 h. Then, calculated the variation (%) of solution stability for the average area at each time interval. We got % of variation of solution stability is 100±5%. Hence, based on these data five OVI standard solution in Levocloperastine Fendizoate API was stable up to 48 h. The corresponding data are presented in Table 11.

Analysis of marketed formulation by developed method

The validated GC-HS method was applied to the simultaneous determination of the five OVI'S in syrup formulations of Levocloperastine Fendizoate (Esticof-LVP and Drycotus). After analysis is completed to calculate the five OVI'S content and the results are shown in Table 12. These results confirmed the amount of each OVI is within the specified limits. No extra peaks which could interfere with the determination of the five OVI'S were observed. Therefore, the proposed method can be confidently employed for the quality control syrups containing the pharmaceutical five OVI'S. Hence, it can be used in the routine quality control of dosage form in industries.

DISCUSSION

Due of toxicity, quantification conferring to the established standards of residual organic solvents in the ultimate pharmaceutical formulation is mandatory for the launch of the market formulation. Any residual organic solvents may already be present in the finished substance, even after the last phase of the development procedure. These facts justify the need for certain attempts to measure the residual organic solvents in Levocloperastine Fendizoate drug using gas chromatography separation and then followed by flame ionization detection.

We got good and accepted results in the validated parameters for five OVI'S. The LOQ value for the five OVI'S 210 ppm for methanol, 350 ppm for ethanol, 42 ppm for dichloromethane, 62 ppm for toluene, and 0.4 ppm for benzene were obtained. The %RSD is obtained <10% for system precision, method precision, and ruggedness and robustness. The % of recovery for five OVI'S was 90% to 110%. As per our proposed method, sample and standard solutions were stable up to 48 h. Moreover, this is method is applied for pharmaceutical dosage forms. The content of all five OVI'S came within the specification limits. Hence, our proposed work is when compared with literature works, the proposed method was found to be novel, simple, sensitive, accurate, precise, economical, and rapid for the estimation of five OVI in Levocloperastine Fendizoate API and its pharmaceutical dosage forms.

CONCLUSION

Our proposed work is completely green chemistry approach. Because in the process of drug synthesis and preparation, so many solvents are used. Those used solvents are very harmful for humans and nature. Need to be check the, those solvents are under criteria limit or not as per ICH

guidelines. Hence, reliable and effective gas chromatography coupled with flame ionization mode of detection dependent methodology to detect and evaluate residual chemical solvents methanol, ethanol, dichloromethane, toluene, and benzene simultaneously in Levocloperastine Fendizoate drug was developed and authenticated in this study. The validation parameters (selectivity, system suitability, precision, linear regression, quantification limit, detection limit, accuracy, robustness, ruggedness, and solution stability) for opted five OVI were in line with ICH requirement. The present results revealed that the quality of the Levocloperastine Fendizoate drug sample can be evaluated using the methodology of gas chromatography proposed in this work.

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CONFLICTS OF INTEREST STATEMENT

No conflicts of interest.

AUTHORS CONTRIBUTION

All authors had equal contributions in the literature, methodology, experimental work,

manuscript preparation, data correction, and finalization of manuscript. All the authors read

and approved the manuscript for final communication.

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