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Research Article

DEVELOPMENT AND VALIDATION OF A GAS CHROMATOGRAPHY HEADSPACE METHOD FOR THE SIMULTANEOUS QUANTIFICATION OF SIX ORGANIC VOLATILE IMPURITIES IN SUMATRIPTAN SUCCINATEAPI AND ITS PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Objective: The main aim of this study, to develop a validated analytical method for simultaneous quantification of six organic volatile impurities (OVI) in sumatriptan succinate active pharmaceutical ingredients (API) and its pharmaceutical dosage forms by headspace (HS)-gas chromatography (GC).

Methods: The method development and its validation were performed on a Shimadzu GC-2010 GC system equipped with a flame ionization detector and Teledynetekmar HT3™ HS analyzer. The method involved a thermal gradient elution of six OVI present in sumatriptan succinate API. DB-624, 30 m×0.53 mm, 3.0 µ column is used as a stationary phase and nitrogen gas is used as a carrier gas. The flow rate was 2.8 mL/min and the flame ionization detector temperature is 260°C.

Results: The correlation coefficient (r^2) was not <0.99 at the limit of quantification (LOQ) to 150%. The limit of detection obtained for methanol, acetone, isopropyl alcohol, dichloromethane, benzene, and toluene was found 18.4, 8.8, 5.5, 4.3, 0.04, and 4.2 ppm. The LOQ obtained was 55.8, 26.8, 16.6, 13.0, 0.1, and 12.6 ppm. Accuracy results were obtained from 85 to 115% for six OVI's. Furthermore, verified precision, ruggedness, robustness, solution stability, and pharmaceutical analysis. All the results are found within the acceptable limits.

Conclusion: The method presents a simple and reliable solution for the routine quantitative analysis of organic volatile impurities present in sumatriptan succinate API.

Keywords: Methanol, Acetone, Isopropyl alcohol, Dichloromethane, Benzene, Toluene, Sumatriptan Succinate active pharmaceutical ingredients, Method development and Validation.

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INTRODUCTION

Sumatriptan succinate (Fig. 1) is chemically 3-[2-(dimethylamino) ethyl]-N-methyl- indole-5-methanesulfonamide succinate [1]. Chemical formula is $C_{18}H_{27}N_3O_6S$ and molecular weight is 413.5 g/mol.

Organic volatile chemicals used in synthesis and process chemistry of drug substances. There is an existing International Conference on Harmonization (ICH) guideline for residual solvents in pharmaceuticals (ICH 1997).

LITERATURE REVIEW

A literature survey regarding the quantitative analysis of sumatriptan succinate revealed that attempts were made to the estimation of sumatriptan succinate in bulk and pharmaceutical dosage forms by high-performance liquid chromatography (HPLC) [1,2] and simultaneous estimation of sumatriptan succinate, metoclopramide hydrochloride, and paracetamol by reverse-phase HPLC [3].

In this study, methanol, acetone, isopropyl alcohol (IPA), dichloromethane, benzene, and toluene were taken as a volatile organic impurity (Fig. 2). The specifications for the six organic volatile impurities were taken very low level compared with ICH specifications. The results obtained were validated according to the ICH guidelines.

METHODS

Chemicals and reagents

Methanol (HPLC grade), acetone (HPLC grade), IPA (HPLC grade), dichloromethane (gas chromatography [GC] grade), benzene (HPLC grade), toluene (HPLC grade), and dimethyl sulfoxide (DMSO) (GC grade) were provided by Sigma-Aldrich. Sumatriptan succinate active pharmaceutical ingredients (API) are taken from a local research laboratory. DMSO is used as a diluent and blank.

Apparatus and chromatographic conditions

Chromatography was performed on a Shimadzu chromatographic system equipped with a Shimadzu GC-2010 system with a flame ionization detector (FID), samples were injected through a Teledyne Tekmar HT3™ Headspace (HS). Data acquisition and integration were performed using GC solution software. The instrument parameters described below were set up to determine the organic volatile impurities.

GC conditions

The column was DB-624 3.0 µm film thickness, 30 m, and 0.53 mm. The column flow is 2.8 mL/min injector temperature: 220°C. The detector temperature is 260°C. The oven program is, initial temperature is 40°C hold for 5 min and increase the ramp rate 20°C/min up to 200°C and hold for 12 min. The split ratio is 20:1 and the carrier gas is N_2.

HS conditions

Vial temperature is 90°C, oven temperature is 100°C, transfer line temperature is 110°C, vial equilibration time is 25 min, inject time is 1.0 min, and GC cycle time is 35 min.

Preparation of solutions

Specifications for organic volatile impurities

Methanol is 2000 ppm, acetone is 1000 ppm, IPA is 500 ppm, dichloromethane is 500 ppm, benzene is 2.0 ppm, and toluene is 500 ppm.

Benzene standard stock solution

Weigh and transferred about 250 mg of benzene into a 50 mL of the volumetric flask containing 30 mL of diluent and diluted to volume with diluent. Further taken 1.0 mL of above solution into 100 mL of volumetric flask and diluted to volume with diluent.

Standard solution preparation

Weigh and transferred about each 500 mg of methanol, 250 mg of acetone, 125 mg of IPA, 125 mg of dichloromethane, and 125 mg of toluene into a 100 mL of the volumetric flask containing 70 mL of diluent and diluted to volume with diluent. Further taken 5.0 mL of the above solution and 0.5 mL of benzene stock solution into 50 mL of volumetric flask and diluted to volume with diluent.

The standard HS vials were prepared with 2 mL of the standard solution and seal the vial with aluminum closure (the standard solution concentration was prepared concerning sample concentration).

Preparation of sumatriptan succinate API sample solution (250 mg/mL)

Accurately weighed about 500 mg of sumatriptan succinate API into an HS vial and add 2.0 mL of DMSO was accurately pipetted into the sample vial. The vial was sealed with aluminum closure.

Preparation of sumatriptan succinate tablet solution

Twenty tablets were weighed and powdered. An amount of powder equivalent to 500 mg sumatriptan succinate was accurately weighed and transferred to an HS vial, add 2 mL of diluent and seal with an aluminum septum and crimp the cap.

Calculation

The organic volatile impurity content was calculated from,

$$\text{PPM(OVI)} = \frac{\text{Impurity area in API}}{\text{Impurity area in Standard solution}} \times \frac{\text{Standard Solution Concentration}}{\text{Sample Solution Concentration}} \times 10^6$$

RESULTS AND DISCUSSION

Method development

The GC-HS method has been developed as stepwise strategies.

Column selection

The primary goal of column selection was to resolve a total of six organic volatile impurities which were used during the synthesis and manufacturing of sumatriptan succinate API. Several columns were initially investigated to finalize a single column for the separation and quantitation of organic volatile impurities. Wall-coated capillary columns of various brands with a variety of phases and dimensions have been investigated. The 1st column is DB-1 (30 m length, 0.32 mm i.d, 1.0 µ film thickness). The 2nd column is VF-624 ms (60 m length, 0.32 mm i.d, 1.0 µ film thickness). Moreover, the 3rd column is DB-624 (30 m length, 0.32 mm i.d, 3.0 µ film thickness). In the above the 1st and 2nd columns, the response was found to be comparatively lower and peak shapes were found to be unsatisfactory, and the resolution is not good. However, the 3rd column has given good resolution, tailing, and good peak shapes. Therefore, DB-624 (30 m length, 0.53 mm i.d, 3.0 µ film thickness) proved to be the best column that could fulfill all the needs of the method, those are higher sensitivity, shorter runtime, and higher resolution between the critical pairs.

HS method optimization

The HS method was optimized in such a way that the maximum amount of the organic volatile impurities presents in the sumatriptan succinate API gets evaporated for the detection. For this, the standard and sample vials were heated at 70°C-100ºC for 15-30 min with constant shaking. A combination of sample vial heating at 90ºC with 25 min shaking was found to be suitable for getting a good response.

Method validation

The developed GC-HS method has been validated as per ICH guideline [4].

Specificity

The relative retention time of the six OVI's indicated that they were well separated from each other (Table 1). The typical chromatograms of six organic volatile impurities and sumatriptan succinate API is shown in Fig. 3.

System suitability

System suitability was evaluated by injecting six replicates of standard solution into the chromatographic system as per the test method. The % relative standard deviation (RSD) was calculated for the area of six OVI's. The % RSD of each impurity is not more than (NMT) 15.0%. Results and typical chromatograms are shown in Table 2 and Fig. 4.

Method precision

Method precision was evaluated by preparing the six different preparations of standard solution into the chromatographic system as per the test method. % RSD was calculated for the area of six preparations. The % RSD of each organic volatile impurity is NMT 15.0%. Results and typical chromatograms are shown in Table 3 and Fig. 5.

Linearity at low level for limit of detection (LOD) and limit of quantification (LOQ)

The linearity of the method was determined over the concentration range of 5%, 10%, 15%, 20%, and 25% concerning the sumatriptan succinate API. The LOD and LOQ were calculated from these linearity data and shown in Table 4.

LOD and LOQ

The LOD and LOQ for the proposed method were determined using calibration standards and calculated using 3.3 σ/s and 10 σ/s formulae, respectively. The data and typical chromatograms are as shown in Table 5 and Fig. 6.

Linearity with LOQ

The linearity of the method was determined over the concentration range of LOQ %, 50%, 75% 100%, 125%, and 150%. The correlation coefficient (r^2) of each impurity is not <0.99. The obtained results and typical chromatograms for linearity as shown in Table 6 and Fig. 7.

LOQ-precision

The % RSD of the area obtained from six standard injections at LOQ level was calculated. The % RSD is abstained NMT 15.0%. The obtained results and typical chromatograms for LOQ precision as shown in Table 7 and Fig. 8.

Accuracy

The accuracy was evaluated by the % recoveries of the six organic volatile impurities spiked with the sumatriptan succinate sample API. The acceptance criterion for accuracy was that should be in the range of 85-115%. The results are indicated in Table 8.

LOQ accuracy

The % recovery of each organic volatile impurity at the LOQ level should be within 100±15%. The results are shown in Table 9.

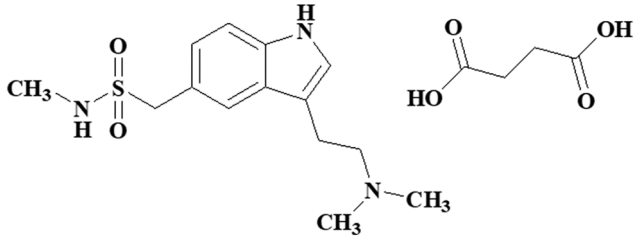

Fig. 1: Chemical Structure of sumatriptan succinate

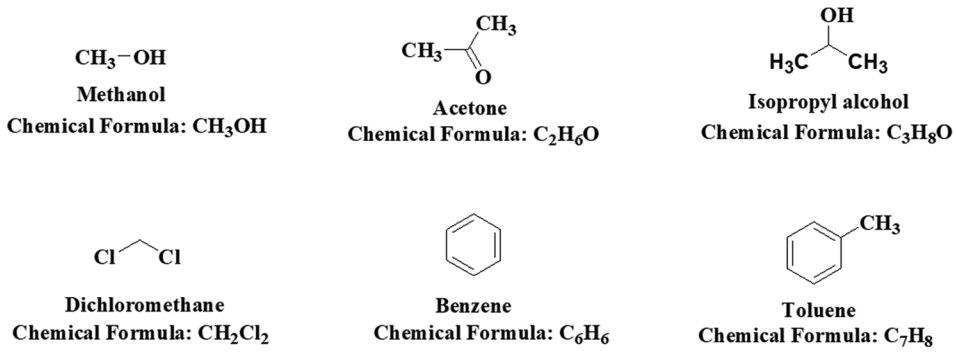

Fig. 2: Chemical structures of six organic volatile impurities

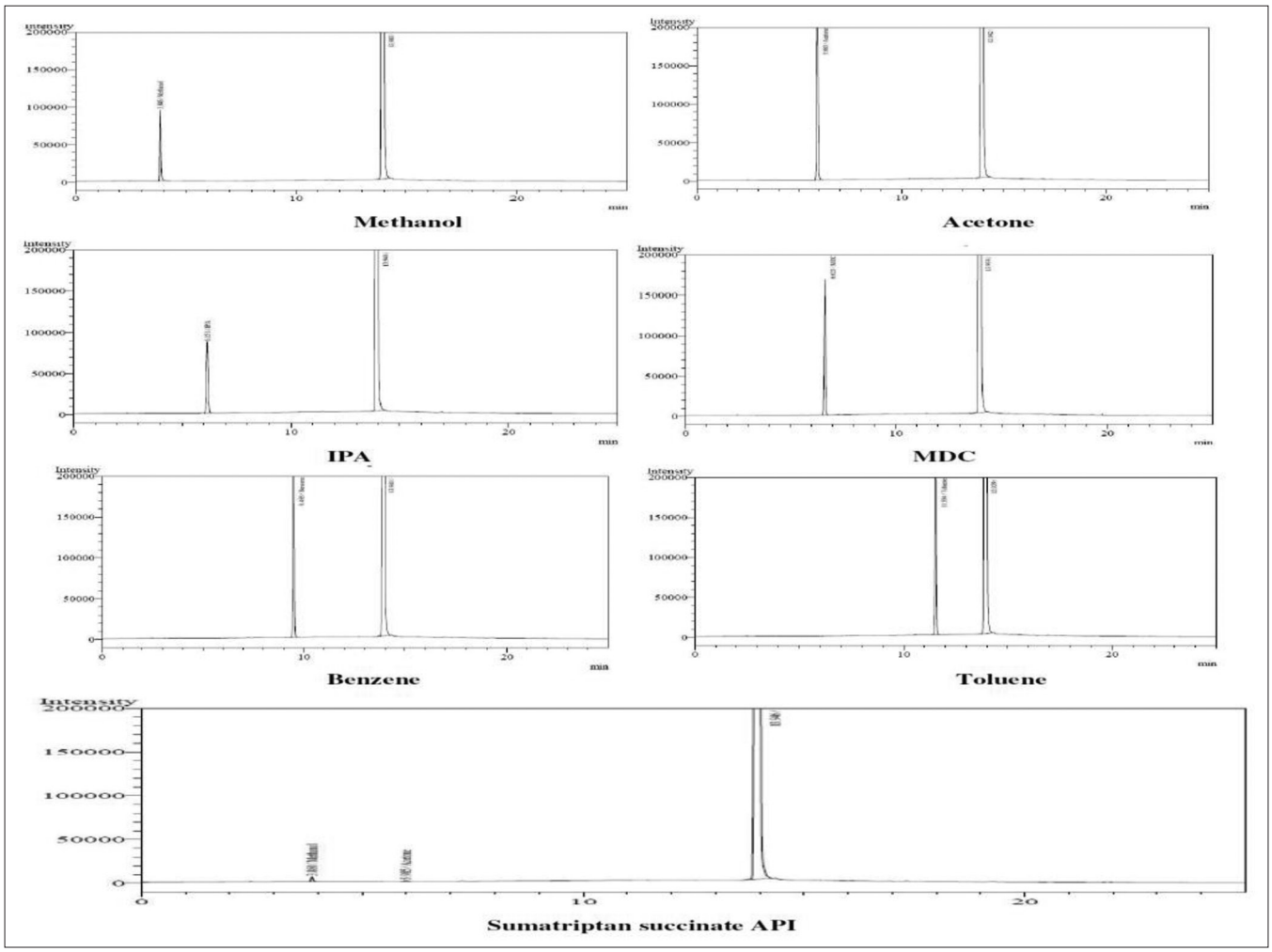

Fig. 3: Typical chromatograms of six organic volatile impurities standard and sumatriptan succinate

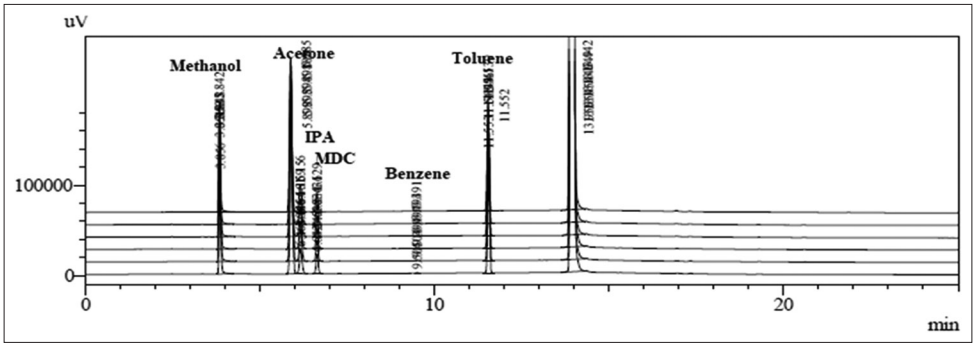

Fig. 4: Typical chromatogram for system suitability

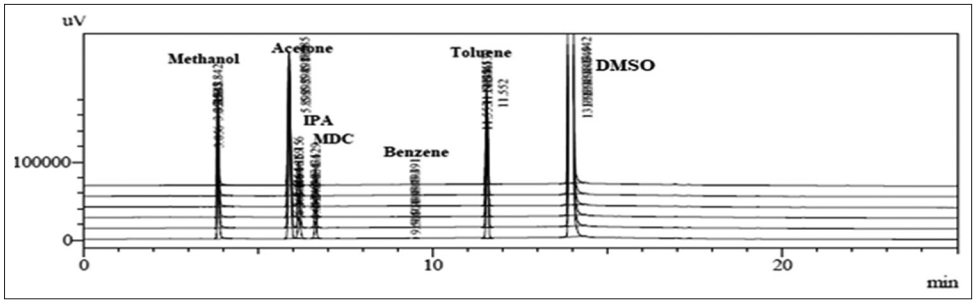

Fig. 5: Typical chromatogram for method precision

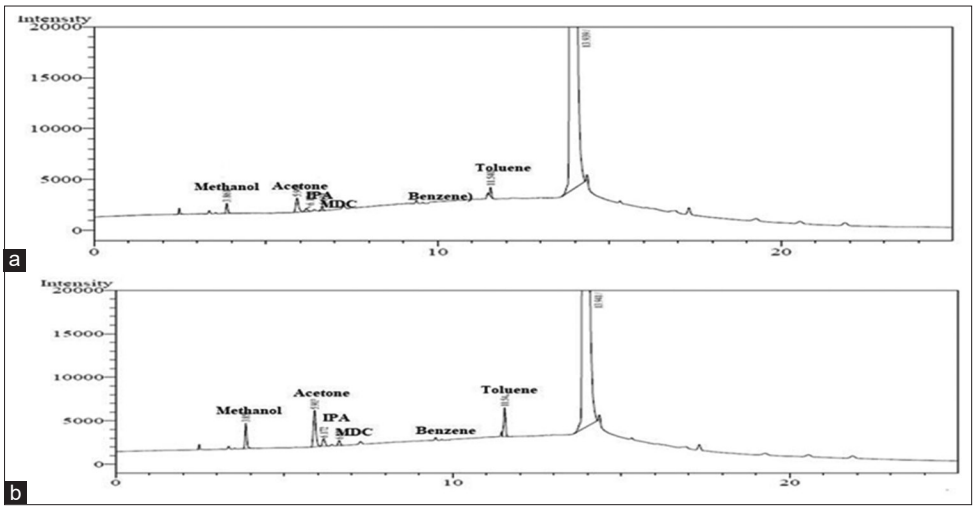

Fig. 6: (a) Limit of detection and (b) limit of quantitation chromatogram of six organic volatile impurities

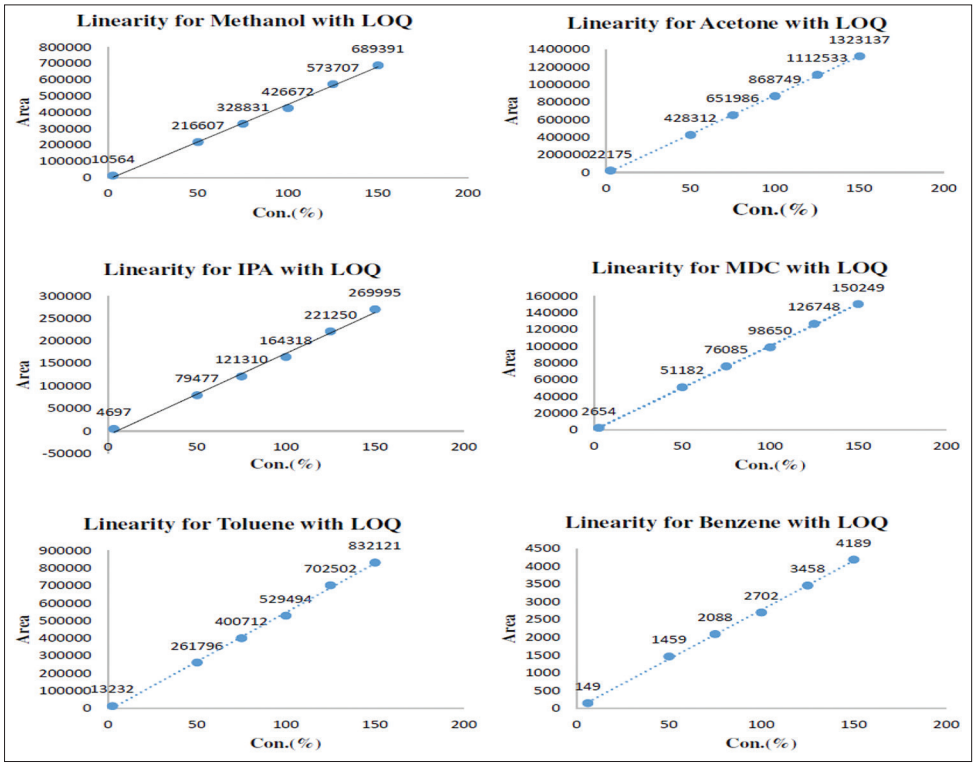

Fig. 7: Linearity with a limit of quantitation graphs of six organic volatile impurities

Table 1: Specificity data for six organic volatile impurities

S. no.	Name of OVI's	RT (min)	Theoretical plates	Tailing factor	USP resolution
1.	Methanol	3.84	31,500	1.24	---
2.	Acetone	5.88	31,592	1.25	18.81
3.	IPA	6.15	31,870	1.24	2.00
4.	MDC	6.62	31,378	1.25	3.63
5.	Benzene	9.49	31,895	1.23	24.58
6.	Toluene	11.53	31,437	1.25	19.28

OVI's: Organic volatile impurities, IPA: Isopropyl alcohol, MDC: Methylene dichloride, USP: United States pharmacopeia

Table 2: System suitability data for six organic volatile impurities

No. of injections	Area of methanol	Area of acetone	Area of IPA	Area of MDC	Area of benzene	Area of toluene
1.	419,110	836,915	157,745	93,538	2588	498,177
2.	387,746	855,404	145,905	95,052	2625	501,092
3.	437,461	857,082	169,561	961,97	2703	527,798
4.	414,158	866,166	158,704	96,748	2702	519,538
5.	494,852	901,815	191,123	103,363	2900	584,455
6	386,431	866,780	144,871	95,838	2654	506,330
AVG.	423,293	864,027	161,318	96,789	2695	522,898
STDV.	40,112	21,437	17,228	3408	110	32,205
RSD (%)	9.48	2.48	10.68	3.52	4.07	6.16

IPA: Isopropyl alcohol, MDC: Methylene dichloride, RSD: Relative standard deviation

Table 3: Method precision data for six organic volatile impurities

No. of injections	Area of methanol	Area of acetone	Area of IPA	Area of MDC	Area of benzene	Area of toluene
1.	549,752	865,575	152,638	97,377	2648	513,474
2.	583,141	883,989	162,296	100,231	2720	541,205
3.	628,288	899,525	177,205	103,111	2962	566,302
4.	594,609	884,003	166,781	99,914	2827	538,721
5.	742,800	937,860	209,916	109,668	3050	625,924
6	650,688	893,877	184,865	102,314	2847	561,709
ACVG.	624,880	894,138	175,617	102,103	2842	557,889
STDV.	67,654	24,340	20,239	4217	149	38,295
RSD (%)	10.83	2.72	11.52	4.13	5.23	6.86

IPA: Isopropyl alcohol, MDC: Methylene dichloride, RSD: Relative standard deviation

Table 4: Low-level linearity data for LOD and LOQ

Con. (%)	Methanol average area (n=2)	Acetone average area (n=2)	IPA average area (n=2)	MDC average area (n=2)	Benzene average area (n=2)	Toluene average area (n=2)
5	18,784	40,776	7099	4796	115	26,659
10	40,563	85,649	15,676	10,151	238	53,845
15	59,479	121,965	23,446	14,456	358	76,261
20	78,221	165,878	30,434	19,422	481	100,954
25	97,106	208,443	38,007	24,346	646	126,971
r^2	1.000	1.000	0.999	1.000	0.998	1.000
STEYX	1084	2223	508	250	16	1242
SLOPE	3886	8311	1531	967	26	4955
LOQ (%)	2.79	2.68	3.32	2.59	6.09	2.51
LOD (%)	0.92	0.88	1.10	0.85	2.01	0.83

LOD: Limit of detection, LOQ: Limit of quantitation, IPA: Isopropyl alcohol, MDC: Methylene dichloride

Table 5: LOD and LOQ data for six organic volatile impurities

OVI's	LOD con. (ppm)	LOQ con. (ppm)	LOD area	LOQ area
Methanol	18.4	55.8	3607	10,564
Acetone	8.8	26.8	7803	22,175
IPA	5.5	16.6	1628	4697
MDC	4.3	13.0	921	2654
Benzene	0.04	0.1	52	149
Toluene	4.2	12.6	2758	13,232

LOD: Limit of detection, LOQ: Limit of quantitation, IPA: Isopropyl alcohol, MDC: Methylene dichloride

Ruggedness

The ruggedness of the method was evaluated by performing the sample analysis in six replicates by different analysts on different days and the results are summarized as shown in Table 10. The % RSD values of six organic volatile impurities are NMT 15.0%.

Robustness

This study was performed by making small variations in the method parameters. The variation in the column flow 2.5 mL/min and 3.1 mL/min, vial condition temperature 75°C and 85°C was done. The obtained % RSD is not more than 15% for every changed method parameter. The results are shown in Table 11.

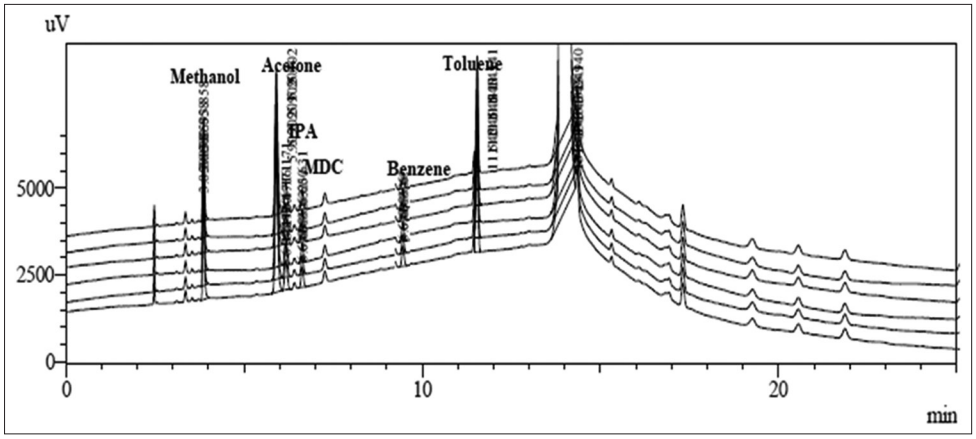

Fig. 8: Limit of quantitation-precision overlay chromatogram for six organic volatile impurities

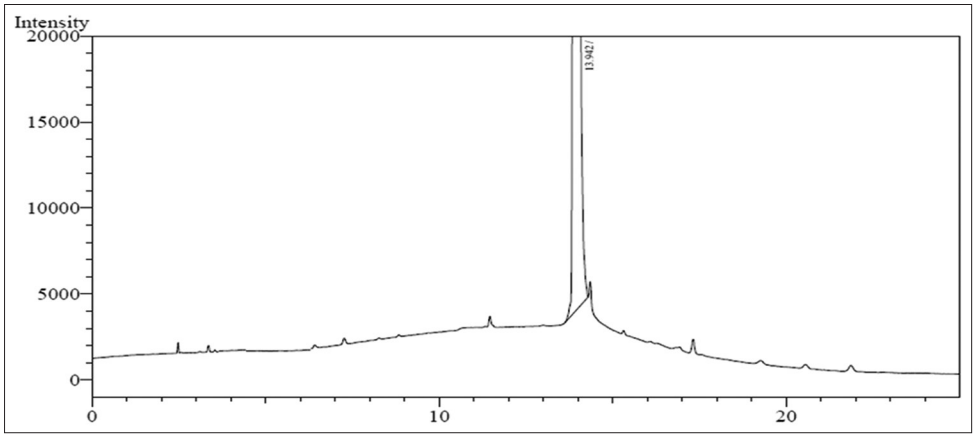

Fig. 9: Typical chromatogram for sumatriptan succinate tablet

Table 6: Linearity data with LOQ

Con. (%)	Methanol average area (n=2)	Acetone average area (n=2)	IPA average area (n=2)	MDC average area (n=2)	Benzene average area (n=2)	Toluene average area (n=2)
*LOQ	10,564	22,175	4697	2654	149	13,232
50	216,607	428,312	79,477	51,182	1459	261,796
75	328,831	651,986	121,310	76,085	2088	400,712
100	426,672	868,749	164,318	98,650	2702	529,494
125	573,707	1,112,533	221,250	126,748	3458	702,502
150	689,391	1,323,137	269,995	150,249	4189	832,121
r^2	0.999	1.000	0.998	1.000	0.999	0.999

*LOQ (%): 2.79% for methanol, 2.68% for acetone, 3.32% for IPA, 2.59% for MDC, 6.09% for benzene and 2.51% for toluene. LOD: Limit of detection, LOQ: Limit of quantitation, IPA: Isopropyl alcohol, MDC: Methylene dichloride

Table 7: LOQ-precision data

No. of injections	Area of methanol	Area of acetone	Area of IPA	Area of MDC	Area of benzene	Area of toluene
Run-1	10441	22071	4752	2609	152	12865
Run-2	9898	22061	4519	2581	155	12990
Run-3	10114	21815	4562	2590	148	12837
Run-4	10134	21907	4600	2542	144	13027
Run-5	11140	21381	5295	2519	160	13208
Run-6	10564	22175	4697	2654	158	13232
ACVG	10382	21902	4738	2583	153	13027
STDV	442	285	286	48	6	166
RSD (%)	4.26	1.30	6.05	1.86	3.98	1.28

IPA: Isopropyl alcohol, MDC: Methylene dichloride, LOQ: Limit of quantitation

Table 7: LOQ-precision data

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Run-2	9898	22061	4519	2581	155	12990
Run-3	10114	21815	4562	2590	148	12837
Run-4	10134	21907	4600	2542	144	13027
Run-5	11140	21381	5295	2519	160	13208
Run-6	10564	22175	4697	2654	158	13232
ACVG	10382	21902	4738	2583	153	13027
STDV	442	285	286	48	6	166
RSD (%)	4.26	1.30	6.05	1.86	3.98	1.28

IPA: Isopropyl alcohol, MDC: Methylene dichloride, LOQ: Limit of quantitation

Table 8: Recovery data for six organic volatile impurities

OVI's	Average sample area (n=3)	Average STD area (n=3)	Average 50% area (n=3)	Average 100% area (n=3)	Average 150% area (n=3)	% recovery at 50, 100, and 150%	
Methanol	20,720	423,293	218,883	448,403	677,886	50	93.63
						100	101.04
						150	103.50
Acetone	6248	864,027	429,669	879,057	1,322,004	50	98.01
						100	101.02
						150	101.52
IPA	ND	161,308	80,444	173,348	264,440	50	99.74
						100	107.46
						150	109.29
MDC	ND	96,789	51,465	100,144	149,711	50	106.34
						100	103.47
						150	103.12
Benzene	ND	2695	1451	2750	4161	50	107.68
						100	102.04
						150	102.93
Toluene	ND	522,898	263,573	543,064	827,234	50	100.81
						100	103.86
						150	105.47

IPA: Isopropyl alcohol, MDC: Methylene dichloride, LOQ: Limit of quantitation

Table 9: Recovery data at LOQ level

No. of injections	Area of methanol	Area of acetone	Area of IPA	Area of MDC	Area of benzene	Area of toluene
Run-1	31,574	29,689	5283	2670	157	14,391
Run-2	31,742	27,624	5277	2775	164	14,530
Run-3	31,674	29,144	5600	2727	152	14,879
Average area	31,663	28,819	5387	2724	158	14,600
STD avg. area (n=6)	10,382	21,902	4738	2583	153	13,027
In sample avg. area (n=3)	20,720	6248	ND	ND	ND	ND
% recovery	105.41	103.05	113.69	105.46	103.05	112.07

IPA: Isopropyl alcohol, MDC: Methylene dichloride, LOQ: Limit of quantitation

Table 10: Ruggedness data for six organic volatile impurities

Different days and analysts		%RSD for methanol	%RSD for acetone	%RSD for IPA	%RSD for MDC	%RSD for benzene	%RSD for toluene
Day-1	Analyst-1	3.91	2.03	3.00	4.37	4.03	3.29
	Analyst-2	7.69	4.53	3.30	5.27	4.4	2.56
	Analyst-1 and 2	5.81	3.64	7.41	4.83	4.21	2.81
Day-2	Analyst-1	7.05	2.09	3.76	8.27	5.86	2.34
	Analyst-2	8.54	3.39	5.06	3.09	5.56	1.53
	Analyst-1 and 2	7.48	2.88	4.52	6.77	5.03	1.93
Analyst-1	Day-1 and 2	6.8	2.32	8.67	6.6	4.83	3.36
Analyst-2	Day-1 and 2	8.48	3.91	4.08	4.92	4.92	3.21

IPA: Isopropyl alcohol, MDC: Methylene dichloride

Table 11: Robustness data for six organic volatile impurities

Name of OVI's	Flow rate (mL/min)		Vial condition temperature (°C)	
	2.5 mL/min (RSD %)	3.1 mL/min (RSD %)	75°C (RSD %)	85°C (RSD %)
Methanol	9.47	5.02	3.84	4.83
Acetone	3.60	1.62	3.19	6.23
IPA	9.66	6.61	6.27	2.86
MDC	5.01	4.72	2.15	3.48
Benzene	5.16	3.05	3.76	2.57
Toluene	2.53	3.04	3.23	3.50

IPA: Isopropyl alcohol, MDC: Methylene dichloride

Table 12: Six organic volatile impurities content in tablet analysis

Name of drug	Label claim (mg)	Methanol (ppm)	Acetone (ppm)	IPA (ppm)	MDC (ppm)	Benzene (ppm)	Toluene (ppm)
Sumatriptan succinate	100	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

IPA: Isopropyl alcohol, MDC: Methylene dichloride

Table 13: Solution stability data for six OVI's and sumatriptan succinate API

Methanol (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	429,510	Not applicable	23,615	Not applicable
At 12	418,456	97.43	23,516	99.58
At 24	409,560	95.36	23,356	99.32
Acetone (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	852456	Not applicable	7325	Not applicable
At 12	839521	98.48	7295	99.59
At 24	824562	96.73	7245	99.31
IPA (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	1658845	Not applicable	Not detected	Not applicable
At 12	1611450	97.14	Not detected	Not applicable
At 24	1601256	96.53	Not detected	Not applicable
MDC (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	94215	Not applicable	Not detected	Not applicable
At 12	92256	97.92	Not detected	Not applicable
At 24	90145	95.68	Not detected	Not applicable
Benzene (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	2645	Not applicable	Not detected	Not applicable
At 12	2515	95.09	Not detected	Not applicable
At 24	2499	94.48	Not detected	Not applicable
Toluene (h)	Area in standard	% solution stability for standard	Area in sample	% solution stability for API sample
At 0	521325	Not applicable	Not detected	Not applicable
At 12	509523	97.74	Not detected	Not applicable
At 24	501236	96.15	Not detected	Not applicable

IPA: Isopropyl alcohol, MDC: Methylene dichloride, OVI's: Organic volatile impurities, API: Active pharmaceutical ingredients

Sumatriptan succinate tablet analysis

The prepared sumatriptan succinate tablet solution (250 mg/mL) was injected. The six organic volatile impurities content in sumatriptan succinate tablets was found within the specifications. The results and typical chromatograms were shown in Table 12 and Fig. 9.

Solution stability

Stability of six organic volatile impurities standard and sumatriptan succinate API sample prepared in DMSO as a diluent. Three-time intervals solutions (initial, after 12 h, and after 24 h) were prepared on the same day and keep them at room temperature. Initial, after 12 h, and after 24 h OVI's standard and sumatriptan succinate API solutions were injected at that time point. Then, the calculated the % of solution stability for the area of initial, after 12 h, and after 24 h injections. The % of solution stability is 100±10%. From these stability results, we can found that six organic volatile impurities standards and sumatriptan succinate API were stable up to 24 h. The corresponding data are presented in Table 13.

CONCLUSION

The six OVI's, methanol, acetone, IPA, dichloromethane, benzene, and toluene, were well separated from each other and quantified by the proposed method. This method was also applied for the quantification of organic volatile impurities in the marketed sumatriptan succinate, which were present in ppm specification limits as per ICH guidelines. The proposed method was validated as per the ICH guidelines and the results revealed that the method was scientifically. This investigation may be helpful to the manufacturers for controlling and minimization of the organic volatile impurities. Moreover, this method was found to be applicable for the routine analysis of the sumatriptan succinate in the pharmaceutical industry.

AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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