ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 09, pp.73263-73270, September, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

STATIC HEAD SPACE GAS CHROMATOGRAPHIC METHOD FOR QUANTITATIVE DETERMINATION OF RESIDUAL SOLVENTS IN CANAGLIFLOZIN API

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ARTICLE INFO

Article History:
Received 24th June, 2018
Received in revised form
17th July, 2018
Accepted 25th August, 2018
Published online 30th September, 2018

Key Words:
Canagliflozin API,
Static GC HS,
Method development,
Validation,
Residual solvent.

ABSTRACT

The pharmaceutical industry is facing a unnerving challenge in the control of impurities; Residual solvents play as an important role in the synthesis of drugs substances; according to the good manufacturing process measuring residual solvents is an integral part of impurities profile assessment for pharmaceutical products and is mandatory for the release testing of all active pharmaceutical ingredients. In synthesing process of canagliflozin API many solvents being used, to analyses these solvent a sensitive static head space gas chromatography (GC HS) with flame ionization detector (FID) method was developed successfully and validated for residual solvents determination of Canagliflozin API. The head space parameters and chromatographic condition, such as split ratio, flow rate and oven program temperature, were optimized to enhance sensitivity and chromatographic resolution. The optimized parameters are 1-methyl-2-pyrrolidone as diluent, equilibration temperature for head space 40°C for 8 min, Oven temperature program 40°C to 200°C with 20°C ramping, Nitrogen carrier gas and DB-624, 30m length and 0.32mm ID, film thickness 1.8 µm a capillary column used. The proposed method was found to be suitable for the determination of ten different residual solvents. The validation results indicate that method is specific, sensitive, accuracy linear and robust, The obtained recovery ranging from 80% to 120% and regression coefficient was higher than 0.999 for all the solvent.

Citation: ***Rajendra Phadke and Dr. Amit Gosar*****, 2018.** "Static Head Space Gas Chromatographic Method For Quantitative Determination Of Residual Solvents In Canagliflozin API", *International Journal of Current Research*, 10, (09), 73263-73270.

INTRODUCTION

Organic solvents play an important role in the pharmaceutical industry, and appropriate selection of the solvents for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility; Because of some physical and chemical properties, the solvents are not completely removed by practical manufacturing process, Usually some small amounts of solvents may remain in the final drug substance they are called as residual solvents also commonly known as organic volatile impurities. Thus, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, If the presence of residual solvents in pharmaceuticals exceeds tolerance limits as suggested by safety data, they may be harmful to the human health and to the environment. That's the reason residual solvents testing become one of the most important parts of quality control in pharmaceuticals and the regulation of residual solvents and methods for residual solvents testing and analysis. Special emphasis will be given to the recent progress of residual solvents analysis and systematic study on residual solvents analysis in pharmaceuticals. Canagliflozin API trade name Invokana or Sulisent is a medication used for the treatment of type II diabetes. It is of the gliflozin class or sub type II sodium glucose transport inhibitors class. This mechanism is associated with a low risk of hypoglycaemia compared to sulfonyl urea derivatives and insulin. In 2017, the FDA concluded that canagliflozin causes an increased risk of leg and foot amputations. In Canagliflozin manufacturing process many chemical and solvent are used. As regulatory requirement those solvent and chemicals to be control in final analysis, hence we need to developed the sensitive method of analysis. For development we use headspace gas chromatography (GCHS), USP incorporated this technique in general chapter "<467> Residual solvents". Different headspace sampling techniques are available, in USP

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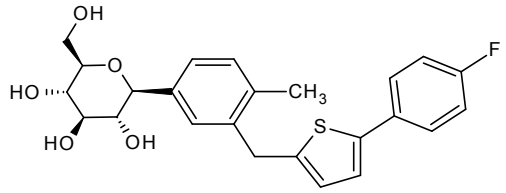
dynamic headspace extraction. A tandem headspace (HS) sampling, gas chromatography (GC) and non-selective detector like flame ionization detector (FID) or selective detector like mass spectrometry detector (MS) is the preferred technique for the analysis of volatile compounds. Flame ionization detector are most of time use for development and it's easily avaible hence we use flame ionization detector with static head space. The details development and optimization parameter are given in method optimization chapter. The structure of canagliflozin API is as below.



Chemical / IUPAC name: (2S, 3R, 4R, 5S, 6R)-2-(3-((5-(4-fluorophenyl) thiophene-2-yl) methyl)-4-methylphenyl)- 6-(hydroxymethyl) tetrahydro-2H-pyran-3, 4, 5-triol

Table 1. List of Solvents used for synthesis of Canagliflozin

Sr. No	Component Name	Class of solvent	Limit
1	Methanol	Class-2	3000 ppm
2	Diethyl ether	Class-3	5000 ppm
3	Acetonitrile	Class-2	410 ppm
4	n- Hexane	Class-2	290 ppm
5	Ethyl acetate	Class-3	5000 ppm
6	Tetrahydro furan	Class-2	720 ppm
7	Cyclohexane	Class-2	3880 ppm
8	Methyl isobutyl ketone	Class-2	4500 ppm
9	Toluene	Class-2	890 ppm
10	Dimethyl formamide	Class-2	880 ppm

MATERIALS

Reagent and Chemicals: Methanol, Diethyl ether, Ethyl acetate, Acetonitrile, n-Hexane, Cyclohexane, Tetrahydrofuran, Methyl isobutyl ketone, Toluene, Dimethyl formamide AR grade were purchased from Merck (India) Limited, and 1-methyl-2-pyrrolidone AR grade purchased from Spectrochem Private Limited. Canagliflozin API provides by analytical research and development of Indoco Remedies Limited, Rabale.

Instrumentation: PerkinElmer, Clarus 500, Gas Chromatograph (GC), with Flame Ionization Detector and Electron Capture Detector, Turbomatrix 40 headspace autosampler, a thermostatic column compartment. Headspace vials with PTFE Septa and Crimp Caps, 22 mL capacity. DB-624 column, 30m length and 0.32mm ID, film thickness 1.8 µm. Data acquisition and calculations were carried out using Total chrome navigator software version 6.3.2.0646 and Sartorius (Germany) analytical balance was used for weighing solvent standard.

METHODS

Method optimization: As mentioned in the background of the invention of Canagliflozin API, Canagliflozin synthesis process we used many of chemical and solvent. As pharmaceutical guideline, international council for harmonisation (ICH) and CGMP these solvent and chemical to be control in final finished product. Therefore need for method development and control of solvent. In method development we use Gas Chromatograph with headspace sampler. Base on solvent miscibility we made mixture of solvents as per our requirement then dilute up to volume with different diluent solvent like Dimethyl sulfoxide, Dimethyl formamide, N-methyl-2-pyrrolidone, Dimethylacetamide, Then further dilute mixture of solvent such a way that the final concentration of solvent meet the limit as per ICH guideline. The selection of column was done by injecting this solvent mixture on different column stationary phases like DB.5(Phenylmethyl dimethylsilicone (10 % phenyl substituted), DB Wax (Polyethylene glycol(average MW 1,500) and DB-625 (6 % Cyanopropylphenyl-94 % dimethylpolysiloxane) and finally FFAB column (Polyethylene glycol TPA (Carbowax 20M terephthalic acid) with different dimension. Base on data outcome we observed that the peak separation are good on DB-624 column, 30m length and 0.32mm ID, film thickness 1.8 µm. Then selection of diluent was done by injecting different diluent, dimethyl formamide diluent was not take because of same solvent need to be control in API, where as dimethyl sulfoxide and dimethyl formamide elute near to same retention time therefore this solvent was not taken as diluent remaining diluent was select base on the raw data of analysis outcome. The finialised solvent was N-methyl-2-pyrrolidone (NMP). Diluent N-methyl-2-pyrrolidone (NMP) peak is not interference at retention time of known solvent peak. The head space parameters was decide base on variation of temperature study. The optimized chromatographic condition details are given in Table 2. For system suitability we injected mixture of solvent at limit level concentration and observed the relative standard deviation, theoretical plate of each solvent and tailing factor of each solvent. The relative standard deviation for replicate injections should not be more than 15 percentages, theoretical plate should not be less than 5000 and trailing factor should not be more than 2. The retention time conformation was done by injecting standard mixture of solvent and then test sample. The details method of analysis are as follows.

Diluent: 1-methyl-2-pyrrolidone (Spectrochem AR grade)

Blank solution: Transfer 1 mL of diluent into a head space vial and seal the vial immediately using PTFE septa. Prepare the blank solution in duplicate.

Standard stock solution: Weigh accurately about 3.0 g of methanol, 5.0 g each of diethyl ether and ethyl acetate, 0.41 g of acetonitrile, 0.29 g of n-Hexane, 3.88 g of cyclohexane, 0.72 g of Tetrahydrofuran, 2.25 g of methyl isobutyl ketone, 0.89 g of toluene and 0.88 g of dimethyl formamide into a 100 mL volumetric flask containing about 20 mL diluent and make upto mark with diluent.

Standard solution: Transfer 2.0 mL standard stock solution into a 100 mL volumetric flask and make upto mark with diluent

System suitability solution: Transfer 1.0 mL of standard solution separately into six head space vials and seal the vial immediately using PTFE/silicon septa.

Test solution: Transfer 0.2 g sample accurately weighed into a head space vial. Add 1.0 mL of diluent and seal the vial immediately using PTFE/silicon septa. Prepare the sample in duplicate.

Chromatographic Conditions

Equipment	Gas Chromatograph
Model	Perkin Elmer, Clarus 500 with head space
Column	DB-624, 30m length and 0.32mm ID, film thickness 1.8 µm or equivalent.
Detector	Flame Ionization Detector
Oven temperature	Initial 40°C, hold for 8.0 minutes Increase @ 20°C per minute to 200°C Hold at 200°C for 4.0 minutes
Detector Temperature	220°C
Injector Temperature	200°C
Attenuation	Initially attenuation -3 till retention time 4.50 min, from 4.51 min to 8.80 min attenuation -6, from 8.81 mins to 11.00 min, attenuation -3, after 11.01 mins. Attenuation -6 to till end
Split Ratio	1:10
Carrier Gas	Nitrogen
Carrier Gas Flow	1.50 mL/min
Run time	20 min
Range	01
Head space conditions	
Ovenequilibration temperature	100°C
Needle temperature	110°C
Transfer line temperature	120°C
Thermostat time	30.0 minutes
Pressurization time	3.0 minutes
Injection time	0.05 minutes
Withdrawal time	0.5 minutes
GC Cycle Time	34.0 minutes

Injection sequence

Sl#	Description	No. of Injections
1	Blank	2
2	System suitability solution	6
3	Blank	2
4	Test solution-1	1
5	Test solution-2	1

Procedure: Condition the column at 200°C for two hours and equilibrate the column at 40°C.

Evaluation of blank: Place the head space vial of the blank solution in the magazine. Inject blank solution and record the chromatogram. Make blank correction if necessary.

Evaluation of standard solution: Inject the standard solution into the chromatograph six times and record the chromatograms. Ensure that system suitability parameters are satisfied.

System suitability

Acceptance criteria

Tailing factor: The tailing factor of each solvent peak should be less than 2.0 in System suitability solution.
Number of Theoretical plates: The number of theoretical plates calculated for each solvent peak for the six replicate injections of System suitability solution should not be less than 5000.
% RSD: The % RSD of six replicates of each individual solvent peak areas should not be more than 15.0 in System suitability solution.

Procedure

Inject again blank solution and test solution in duplicate and record the chromatograms. The retention time of standard solvent should match as given below.

Sl#	Solvents	Retention Time (About in min)
1	Methanol	3.0
2	Diethyl ether	4.3
3	Acetonitrile	5.4
4	n-Hexane	7.0
5	Ethyl acetate	9.2
6	Tetrahydrofuran	9.5
7	Cyclohexane	10.0
8	Methyl isobutyl ketone	12.4
9	Toluene	12.6
10	Dimethyl formamide	13.7

Calculations

Calculate each solvent content for Test solution-1 and Test solution-2 and report the average content by using the following formula:

$$\text{Solvent content (ppm)} = \frac{AT \times WS \times 2 \times 1}{AS \times WT \times 100 \times 100} \times 10^6$$

Where,

AT is peak area of individual solvent in test solution.
AS is average peak area of corresponding solvent in system suitability solution.
WS is weight in g of corresponding solvent for system suitability solution.
WT is weight in g of sample in test solution preparation.

ANALYTICAL METHOD VALIDATION

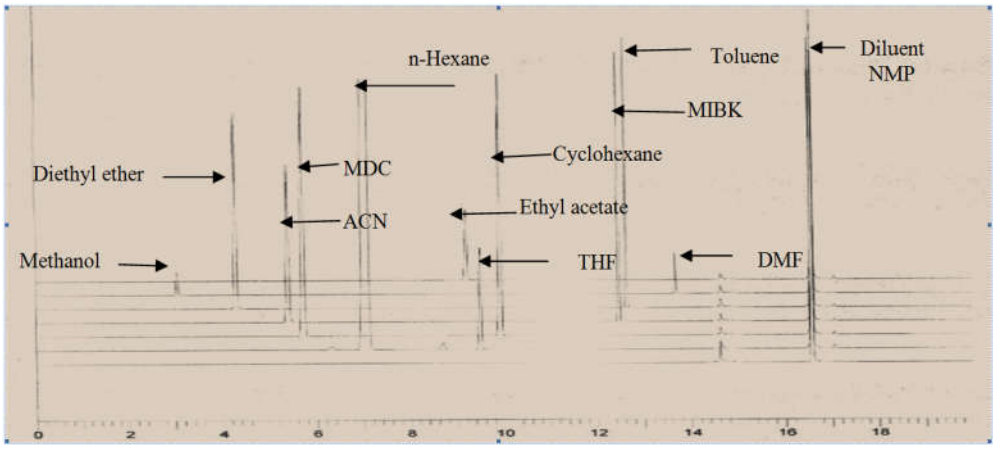
The developed method is subjected to analytical method validation, which is conducted according to the International Council for Harmonisation (ICH) guidelines [5-10]. The parameter which was taken for analytical method validation as specificity, limit of detection, limit of quantitation, linearity, accuracy, precision and robustness.

RESULTS AND DISCUSSION

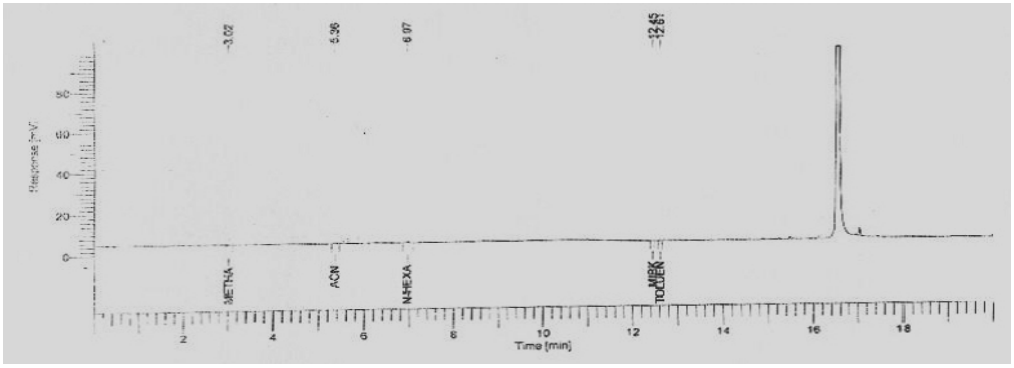
System suitability: The system suitability test represents as an integral part of the method and used to ensure adequate performance of the chromatographic system. To check the system suitability, inject mixture of standard solvent and observed the peak tailing factor, number of theoretical plates, percentage relative standard solution of replicate standard injection. The area details of each solvent peak, relative standard deviation and theoretical plate were recorded in Table 2. The percentage relative standard deviation should be less than 15.0, tailing factor should not be more than 2.0 and the theoretical plate should not be less than 5000. The system suitability was checked before each validation parameter.

Specificity: Specificity is the capability of the method to measure the response of solvent in the presence of drug substance and its impurities. Figure 1 shows the typical chromatograms of the blank as 1-methyl-2-pyrrolidone, Standards of solvent, Test sample and mixture of standard solvent. The results indicated that all solvent are well separated under the optimized chromatographic conditions. Also, there was no interference of peaks due to blank solution and the samples solution within the retention time of solvent peak obtained. Each solvent peak are well separated from each other and each solvent has different retention time. The retention times of each solvent refer Table 3.

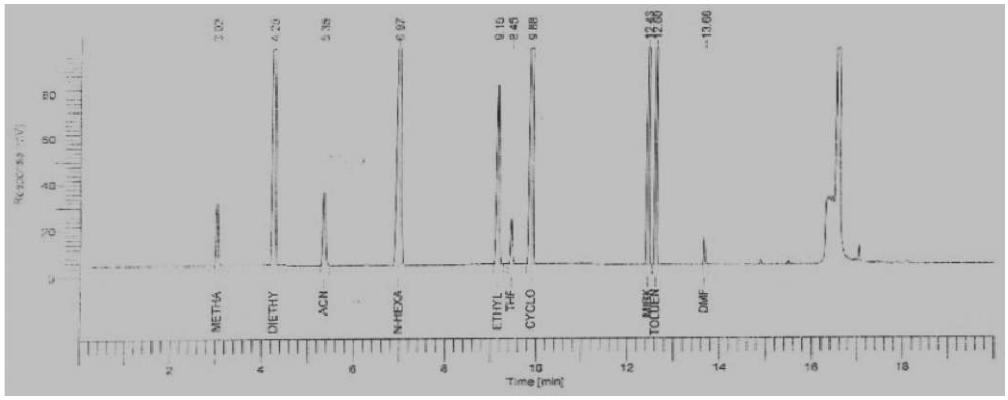
Typical chromatrogram



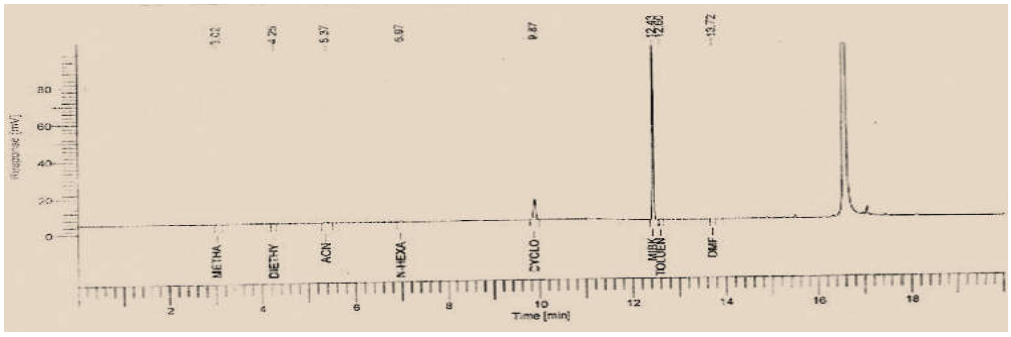
(A)



(B)



(C)



(D)

Figure. 2. Specificity

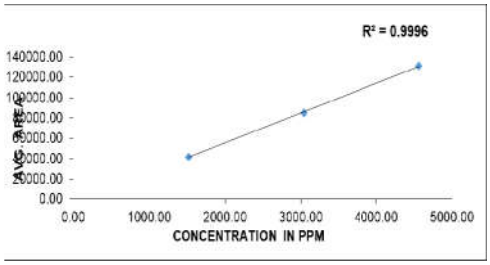
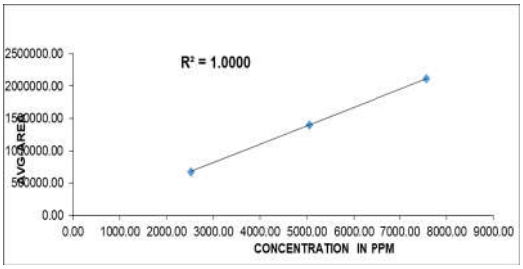
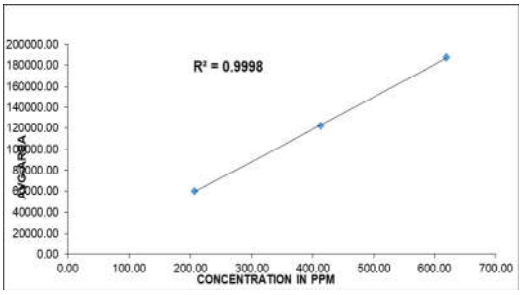
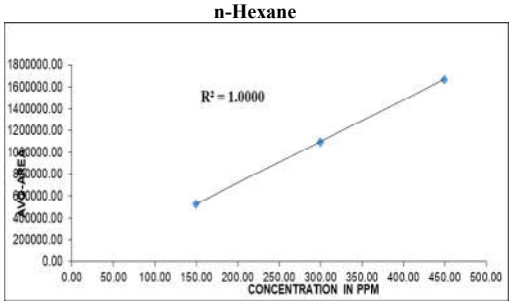
Table 3. Retention time of Solvent

Sr No.	Solvent	RT
1	Methanol	3.02
2	Diethyl ether	4.24
3	Acetonitrile	5.34
4	n- Hexane	6.96
5	Ethyl acetate	9.15
6	Tetrahydro furan	9.45
7	Cyclohexane	9.88
8	Methyl isobutyl ketone	12.43
9	Toluene	12.60
10	Dimethyl formamide	13.66

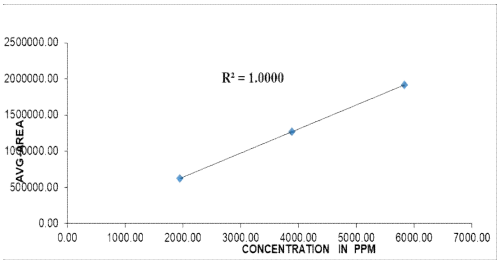
Table 4. Limit of detection and quantitation

Sr.No	Solvent	RT	LOD in ppm	LOQ in ppm
1	Methanol	3.02	3.98	13.27
2	Diethyl ether	4.26	0.48	1.61
3	ACN	5.36	0.48	1.60
4	n-hexane	6.98	0.06	0.19
5	Ethyl acetate	9.16	2.13	7.11
6	THF	9.46	1.22	4.07
7	Cyclohexane	9.89	0.41	1.36
8	MIBK	12.44	0.28	0.93
9	Toluene	12.61	0.16	0.55
10	DMF	13.67	3.30	11.00

Table 05. Linearity figures and Results

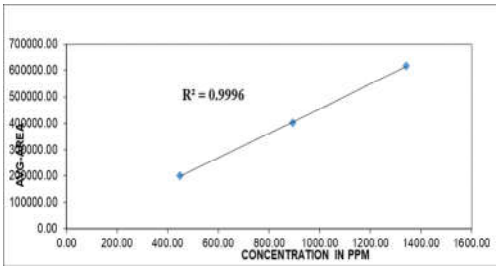
Methanol		**Diethyl Ether**	
			
Slope	**29.51**	**Slope**	**284.15**
Intercept	**-3623.09**	**Intercept**	**-39207.10**
%y-Intercept	**-4.24**	**%y-Intercept**	**- 2.80**
Regression coefficient (R^2)	**0.9996**	**Regression coefficient (R^2)**	**1.0000**
Acetonitrile		**n-Hexane**	
			
Slope	**307.31**	**Slope**	**3805.93**
Intercept	**-3641.38**	**Intercept**	**-41634.02**
%y-Intercept	**-2.9808**	**%y-Intercept**	**-3.79**
Regression coefficient (R^2)	**0.9998**	**Regression coefficient (R^2)**	**1.0000**

Cyclohexane



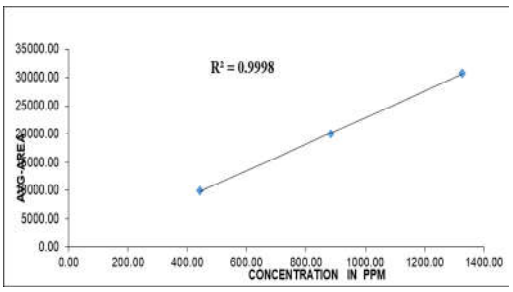
Slope	332.40
Intercept	-20546.08
%y-Intercept	-1.6190
Regression coefficient (R^2)	1.0000

Toluene



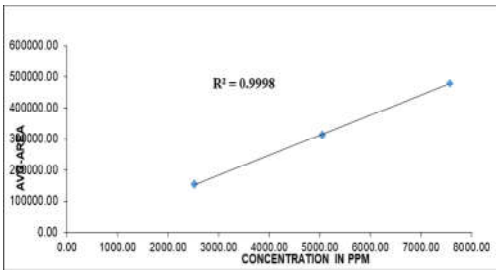
Slope	464.35
Intercept	-8318.46
%y-Intercept	-2.067
Regression coefficient (R^2)	0.9996

DMF



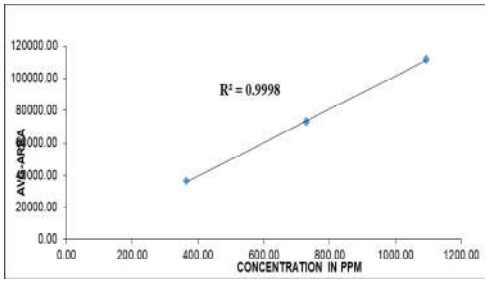
Slope	23.55
Intercept	-587.90
%y-Intercept	-2.93
Regression coefficient (R^2)	0.9998

Ethyl Acetate



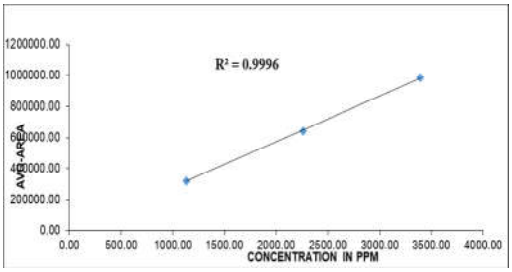
Slope	63.99
Intercept	-7068.82
%y-Intercept	-2.26
Regression coefficient (R^2)	0.9998

THF



Slope	103.29
Intercept	-1609.36
%y-Intercept	-2.204
Regression coefficient (R^2)	0.9998

MIBK



Slope	293.15
Intercept	-12751.72
%y-Intercept	-1.98
Regression coefficient (R^2)	0.9996

Table 6. System precision and precision at LOQ

Parameter :System precision		Parameter : LOQ precision	
Peak name	% RSD	Peak name	% RSD
Methanol	1.20	Methanol	1.50
Diethyl ether	1.67	Diethyl ether	2.40
ACN	0.90	ACN	1.02
n-hexane	1.77	n-hexane	1.85
Ethyl acetate	1.06	Ethyl acetate	1.52
THF	1.06	THF	1.08
Cyclohexane	1.26	Cyclohexane	2.20
MIBK	1.24	MIBK	2.50
Toluene	1.24	Toluene	2.40
DMF	2.54	DMF	3.50

Table 07. Recovery of Impurities-50%

Sr #	Solvent	Standard Area	Sample Area	Corr. Spl area	Standard Wt (g)	Sample Wt (g)	Content (ppm)	% Recovery
1	Methanol	88034.96	45596.00	45017.37	3.03904	0.10061	3089.23	101.16
2	Diethyl Ether	1416439.14	747885.23	747885.23	5.04838	0.10044	5307.77	105.14
3	ACN	128111.13	66456.23	65112.81	0.41271	0.10057	417.14	99.38
4	MDC	88300.63	48356.58	48356.58	0.60426	0.10012	661.04	109.40
5	N-Hexane	1113136.52	602903.28	600841.17	0.29970	0.10064	321.48	106.93
6	Ethyl Acetate	324344.33	171245.13	171245.13	5.04433	0.10045	5302.68	105.12
7	THF	75739.89	38109.36	38109.36	0.72834	0.10057	728.79	100.06
8	Cyclohexane	1296847.21	714716.68	714716.68	3.88632	0.10069	4254.29	109.13
9	MIBK	668791.12	450923.16	450923.16	2.26086	0.10071	3027.21	107.80
10	Toluene	418656.99	222801.45	222197.39	0.89475	0.10066	943.53	105.45
11	DMF	21877.14	9742.13	9465.83	0.88415	0.10042	784.15	88.69

Table 08. Recovery of Impurities-100%

Sr #	Solvent	Standard Area	Sample Area	Corr. Spl area	Standard Wt (g)	Sample Wt (g)	Content (ppm)	% Recovery
1	Methanol	88034.96	139409.23	138830.60	3.03904	0.30198	3174.08	103.95
2	Diethyl Ether	1416439.14	2281560.23	2281560.23	5.04838	0.30147	5394.76	106.86
3	ACN	128111.13	203123.98	201780.56	0.41271	0.30145	431.27	102.80
4	MDC	88300.63	151109.10	151109.10	0.60426	0.30178	685.31	113.41
5	N-Hexane	1113136.52	1843350.06	1841287.95	0.29970	0.30170	328.64	109.32
6	Ethyl Acetate	324344.33	531890.22	531890.22	5.04433	0.30142	5488.80	108.81
7	THF	75739.89	116219.47	116219.47	0.72834	0.30137	741.68	101.83
8	Cyclohexane	1296847.21	2186602.01	2186602.01	3.88632	0.30140	4348.17	111.55
9	MIBK	668791.12	1392398.49	1392398.49	2.26086	0.30188	3118.48	111.84
10	Toluene	418656.99	695561.92	694957.86	0.89475	0.30149	985.28	110.12
11	DMF	21877.14	30872.75	30596.45	0.88415	0.30157	827.47	93.59

Table 09. Recovery of Impurities-150%

Sr #	Solvent	Standard Area	Sample Area	Corr. Spl area	Standard Wt (g)	Sample Wt (g)	Content (ppm)	% Recovery
1	Methanol	88034.96	92386.86	91808.23	3.03904	0.20132	3148.52	103.11
2	Diethyl Ether	1416439.14	1515632.30	1515632.30	5.04838	0.20132	5366.50	106.30
3	ACN	128111.13	135241.10	133897.68	0.41271	0.20132	428.52	102.14
4	MDC	88300.63	98732.12	98732.12	0.60426	0.20132	671.21	111.08
5	N-Hexane	1113136.52	1224904.04	1222841.93	0.29970	0.20132	327.08	108.80
6	Ethyl Acetate	324344.33	350594.81	350594.81	5.04433	0.20132	5416.84	107.38
7	THF	75739.89	77010.98	77010.98	0.72834	0.20132	735.71	101.01
8	Cyclohexane	1296847.21	1451031.34	1451031.34	3.88632	0.20132	4319.86	110.82
9	MIBK	668791.12	920864.33	920864.33	2.26086	0.20132	3092.59	110.69
10	Toluene	418656.99	460367.94	459763.88	0.89475	0.20132	976.16	109.10
11	DMF	21877.14	19912.53	19636.23	0.88415	0.20132	799.48	90.42

Limit of detection and limit of quantitation: A mixture of standard solvents of minimum concentration was injected and calculate the signal to noise ratio base on instrumental method and report the results. To verify further inject a series of standard solutions and subjected to head space and calculate the Limit Of Detection (LOD) and Limit Of Quantitation (LOQ), based on linearity regression line i.e residual standard deviation (STE_{YX}) and slope. The calculated LOD and LOQ are well within limit as per ICH guideline and it show lowest 0.06ppm as LOD and 13.27 ppm as LOQ for all the Solvent (Table 4).

Linearity: A serial dilution of standard solution were prepared from 50% to 150% of target concentration. The linearity curves were drawn by plotting the peak response of standard solvent against its corresponding concentration. The plotted the graph area against test concentration. The regression coefficient, slope and % y intercept are calculate and reported in Table 5. Observed regression coefficient should be greater than 0.999 and % y intercept was less than 5.0%.

Precision: System precision was an integral part of instrument and its working satisfactory. This was carried out by injecting six standard solutions at limit level concentration. Where as in LOQ precision, LOQ concentration was injected reputedly and check the precision with respected to concentration.

The relative standard deviation for standard solution was found to be 2.54% and for LOQ level, standard deviation was below 3.50 % (Table 6).

Accuracy: Accuracy of the method was established by carrying out the recovery of solvent in test sample.The test sample was spiked with standard solvent at specific limit level concentrations 50%, 100% and 150%. Each spiked test solution was analyzed for recovery study and observed the percentage recovery. Recovery obtained for doped solvent should be between 80% to 120% (Table 7, 8 and 9).

Conclusion

A single, rapid and highly selective GC Headspace method was developed and validated for the quantities determination of residual solvents present in Canagliflozin bulk drug through an understanding of the synthetic process, nature of solvents and nature of stationary phases of columns. The residual solvents Methanol, Diethyl ether, Acetonitrile, n- Hexane, Ethyl acetate, Tetrahydrofuran, Cyclohexane, Methyl isobutyl ketone, Toluene, Dimethyl formamide were determined. The method was shown to be specific, liner, accurate and precise for Canagliflozin API and was applied successfully to monitor and control these solvents on a manufacturing level. The

method was found to be applicable for the routine analysis of the Canagliflozin API in pharmaceutical industry.

Acknowledgment

The author wishes to thank to the management of Indoco Remedies Limited for supporting this work by providing the samples of Canagliflozin API and Solvent Standard required for this research.

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