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Research Article

Novel Method for Quantification of Residual Solvent by Head-Space Gas Chromatography for Phenylephrine Hydrochloride USP

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ABSTRACT

The manufacturing process of phenylephrine hydrochloride drug substance contains the use of different solvents in synthesis. USP monograph doesn't provide a method for the residual solvents of active pharmaceutical ingredients (API) as the usage of solvents in the manufacturing process depends on the route of synthesis. Thus, a novel method has been developed and validated as per ICH guidelines for the quantification of solvents in APIs. The method has been developed for the quantification of ethanol, methanol and isopropanol residual solvents present in phenylephrine hydrochloride USP by head-space gas chromatography (HS-GC) using Agilent GC-7890B with HS-7697A and Restek MXT-502.2 (diphenyl/dimethyl polysiloxane) 105 m x 0.53 mm x 3.0 µm column. The method has been validated according to ICH Q2R2 guidelines with validation parameters including specificity, linearity, limit of detection (LoD), limit of quantification (LoQ), precision (System precision, method precision, LoQ precision), and accuracy. The system precision obtained the %RSD of 2.5, 2.7 and 2.7 and the LoQ was established as 23.5. 39.0 and 16.4 ppm, respectively for ethanol, methanol and isopropanol. The LoD of 7.7 ppm, 12.8 ppm and 5.4 ppm for ethanol, methanol and isopropanol indicated the sensitivity of the method for the detection of analytes. The linearity range of 1 to 100% level of specification revealed the correlation coefficient of 0.9987, 0.9978, and 0.9991, respectively for ethanol, methanol and isopropanol solvents.

Introduction

Phenylephrine is the hydrochloride salt form of phenylephrine and acts as an alpha-1 adrenergic receptor agonist. It shows minimal to no beta-adrenergic activity.[1] It is categorized as the class of mydriatic, nasal decongestant and cardiotonic agent. The molecular weight of phenylephrine hydrochloride is 203.66 g/mol and has a molecular formula of $C_9H_{14}CINO_2$.[2] Phenylephrine hydrochloride is formulated in different dosage forms such as tablets, syrup, solution, ophthalmic drops, etc.[2] The manufacturing process of API goes through different stages of chemical reactions and synthesis in the presence of solvents. Thus, USP monographs of API including phenylephrine HCl USP monograph do not provide a procedure for the quantification of residual solvents by head-space gas chromatography.[3] The control of residual solvents present in the drug substance and drug product is necessary and mandatory as per current FDA & USP guidelines.[4] Thus, the risk assessment report for residual solvent must be submitted to the FDA evaluating the toxicity of the present solvent as per permitted daily exposure (PDE) provided in USP for each category of solvents.[5] Hence, the method for the quantification of ethanol, methanol and isopropanol residual solvents in phenylephrine hydrochloride USP has been developed[6,7] by executing various columns and instrumental parameters.[8] However, there were some challenges to developing methods without solvent interference in the analysis.[9-14] Thus, the method was developed with minimal interferences of solvent at analyte retention time and validated as per ICH Q2R(2) guidelines for specificity, system precision, method precision,

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LoQ precision, linearity and accuracy.[15] The validated method ensures its capability, consistency, and accuracy in the detection and quantification of solvents in cGMP-regulated environments. As a result, it provides adequacy in pharmaceutical quality control with assurance on the control and risk assessment of residual solvents.

Materials And Methods

The analytical method was developed using Restk MXT-502.2 (Diphenyl/Dimethyl Polysiloxane) 105 m x 0.53 mm x 3.0 µm on Agilent GC-7890B with HS-7697A.[16,17] Dimethyl formamide was utilized as a diluent and ethanol, methanol and isopropanol (Isopropyl Alcohol) standards of 500, 300 and 500 ppm were prepared with respect to specification concentrations of 5000, 3000 and 5000 ppm).

Instruments and Chemicals

Analytical balance – Mettler Toledo AT261, Sonicator – Fisher Scientific FS28, HS-GC – Agilent GC 7890B with HS-7697A. Dimethyl formamide (DMF) – HPLC/GC grade, isopropanol – HPLC/GC grade [Purity: 99.9, 99.98%], ethanol – HPLC/GC grade [Purity: 99.91, 99.95%], methanol – HPLC/GC grade [Purity: 99.99%], phenylephrine hydrochloride USP – 99.9%

Chromatographic Conditions

GC with FID detector and headspace sampler. Column: Restek MXT-502.2 (diphenyl/dimethyl polysiloxane) 105 m × 0.53 mm × 3.0 µm or equivalent. Injector Temperature: 200°C, Detector Temperature: 250°C, Carrier gas: Nitrogen, pressure: 8.0 psi, split ratio: 1:3, purge flow: 3 mL/minute, Makeup: 25 mL/minute, Hydrogen: 40 mL/minute, Zero air: 400 mL/minute, colum temperatures: 70°C Hold for 0 minutes, Rate – 5°C/minute to temperature 200°C with holding time of 10 minutes, rate – 10°C/minute to temperature 240°C for 10 minutes, oven (Incubation) temperature: 85°C, loop temperature: 100°C, transfer line temperature: 110°C, Vial equilibrium time: 30 minutes, Sample injection time: 0.5 minutes GC cycle time: 60 minutes.

Preparation of Solutions

Preparation of diluent

Use DMF as diluent

Preparation of individual stock solution

Weighed and transferred ethanol-1000 mg, methanol-600 mg and isopropanol-1000 mg in individual 20 mL of volumetric flask which contains 10 mL of DMF. Made up the solution up to mark with DMF and mixed well.

Common stock standard

In 5.0 mL of individual stock solution was transferred into a common 100 mL volumetric flask. Made up the solution up to the mark with DMF and mixed well.

Standard solution

Over 10.0 mL of common stock solution was transferred into 50 mL volumetric flask, diluted the solution up to the mark with DMF and mixed well.

Transferred 5.0 mL of the common stock standard into 20 mL headspace vials. Sealed with septum and crimped with aluminum cap.

(Concentrations of Ethanol, Methanol and Isopropanol are about 500, 300 and 500 ppm, respectively)

Preparation of sample

Weighed and transferred about 0.5 g sample into a 20 mL headspace vial. Added 5.0 mL dimethyl formamide, immediately sealed with a septum, crimped cap and mixed gently.

Calculation

Calculate individual solvent by using the following formula,

Au = Area of individual solvent peak in sample solution.

As = Average area of peak corresponding of each solvent standard solution.

W_S = Weight of Standard in g

Wt = Weight of sample in g

P = Potency of standard (% as is)

System Suitability

%RSD for area of all individual solvent p eaks from six injections of standard solution – NMT 15.0%.

Results And Discussion

Specificity

The diluent solution, standard solutions (500 ppm of ethanol, 300 ppm of methanol and 500 ppm of isopropanol) and sample solution were injected and the chromatograms for any interference from diluent solution. The system suitability criteria were within the limit. Interference was observed at RT of methanol and isopropanol peaks (~ 1.4 and 0.2% with respect to % of standard) which were subtracted from the solvent area (Refer Fig. 1) in standard and sample areas. No interference at the retention time of ethanol peaks. The retention times (RT) of methanol, ethanol, and isopropanol peaks in standard solution and in individual stock solution are similar (Refer Figs 1, 2 and 3). Specificity results are mentioned in Table 1.

Limit of Detection and Quantification

The limit of detection (LoD) provides the sensitivity of analyte detection and limit of quantitation (LoQ) provides the capability of quantification at low-level analyte in the method. LoQ and LoD were determined by standard deviation methods. Prepared the solutions of level 1% to 100% for each solvent as mentioned in Table 2.

Where, σ = residual standard deviation

Table 1: System suitability & diluent interference results

Peak areas of analytes for replicated injection of standard solutions			
Injection number	*Methanol*	*Isopropanol*	*Ethanol*
1	1232	2198	2190
2	1191	2116	2108
3	1211	2164	2155
4	1260	2252	2244
5	1195	2116	2112
6	1180	2104	2099
Average	1212	2158	2151
%RSD	2.5	2.7	2.7
Specification	Not more than 15.0%		

Diluent interference results		
Parameter	*Results*	
Blank (Diluent)	Interference found at RT of methanol and isopropyl peak so subtract the area of blank from methanol and isopropyl alcohol area. No interference at retention time of ethanol peak.	
Name of component	RT in standard solution (minute)	RT in individual stock solution (minute)
Methanol	9.792	9.800
Isopropanol	11.241	11.244
Ethanol	10.605	10.615

Table 2: Linearity level

Level (%)	*mL of Solution-A*	*Diluted to mL*	*Concentration (ppm)*		
			Ethanol	*Methanol*	*Isopropanol*
1	0.2	100	5.0	3.0	5.0
2	0.2	50	10.0	6.0	10.0
4	0.2	25	20.0	12.0	20.1
10	0.5	25	50.0	30.0	50.4
25	1.0	20	124.9	75.2	126.0
50	2.0	20	249.9	150.4	252.0
75	3.0	20	374.9	225.6	378.0
100	10.0	50	499.9	300.8	504.0

Preparation of LoQ/LoD Solutions

Accurately weighed and transferred 1001.0, 603.0, and 1009.1 mg of ethanol, methanol and isopropanol standards, respectively in individual 20 mL of volumetric flask which contains 10 mL of DMF. Made up the solution to mark with DMF and mixed well. Transferred 5.0 mL of individual stock solution into a common 100 mL volumetric flask which contains 10 mL of DMF. Made up the solution with diluent and mixed well (Designated as Solution-A).

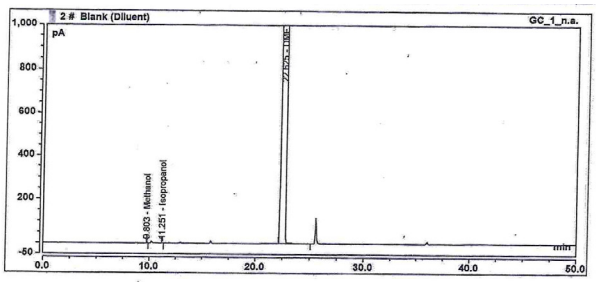
The signal-to-noise ratio is more than 10 for the predicted LoQ level as mentioned in Table 3. The LoQ was determined as 23.5, 39.0 and 16.4 ppm and LoD of 7.7, 12.8 and 5.4 ppm, for respectively ethanol, methanol and isopropanol solvents. Its low-level detection limit ensures the capability of the method and reliability.

Linearity

Linearity of the detector response for solvents was studied from LoQ level to 150% of the specification limit of individual solvents as mentioned in Table 4.

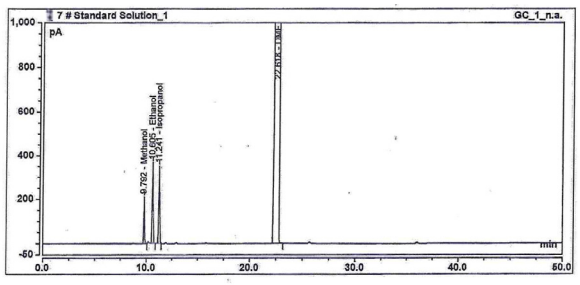
Preparation of Linearity Solutions

Accurately weighed and transferred 1001.0, 603.0, and 1009.1 mg of ethanol, methanol and isopropanol standards,



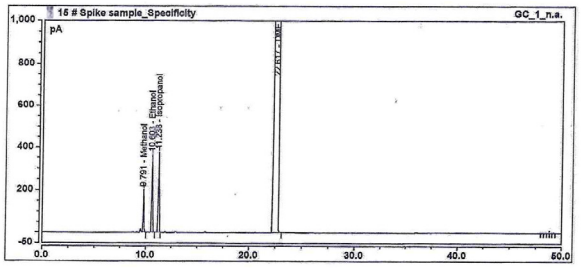
Peak No	Peak Name	Ret.Time min	Area pA*sec	Area %
1	Methanol	9.803	17	0.005
2	Isopropanol	11.251	4	0.001
3	DMF	22.625	330756	99.994
		Total :	330777	100.000

Fig. 1: Typical chromatogram of blank



Peak No	Peak Name	Ret.Time min	Area pA*sec	Area %
1	Methanol	9.792	1249	0.364
2	Ethanol	10.605	2190	0.639
3	Isopropanol	11.241	2202	0.643
4	DMF	22.618	337021	98.354
		Total :	342661	100.000

Fig. 2: Typical chromatogram of standard



Peak No	Peak Name	Ret.Time min	Area pA*sec	Area %
1	Methanol	9.791	1170	0.341
2	Ethanol	10.603	2165	0.632
3	Isopropanol	11.238	2323	0.678
4	DMF	22.617	336994	98.349
		Total :	342652	100.000

Fig. 3: Typical chromatogram of spiked sample

respectively in individual 20mL of volumetric flask which contains 10 mL of DMF. Made up the solution up to mark with DMF and mixed well. Transferred 5.0 mL of individual stock solution into a common 100 mL volumetric flask that contains 10 mL of DMF. Diluted the solution with DMF and mixed well (Designated as Solution-A).

The correlation coefficient for ethanol, methanol and isopropanol were established as 0.9987, 0.99778 and 0.9991, respectively when calculating response against the concentration. Thus, the data shows the method is linear. The linearity results are depicted in Tables 5 to 7 and Figs 4 to 6.

Table 3: Results for LoQ-LoD Prediction

Ethanol		
Concentration (ppm)	*Areas*	
5.0025	16	
10.0050	36	
20.0100	79	
50.0250	196	
125.0624	528	
250.1249	1019	
Slope	4.1169	
Residual standard deviation	9.6749	
	ppm	*S/N* at LoQ
LoD	7.7	69.6
LoQ	23.5	
Methanol		
Concentration (ppm)	*Areas*	
3.0147	114	
6.0294	106	
12.0588	133	
30.1470	184	
75.3675	392	
150.7349	659	
Slope	3.8133	
Residual standard deviation	14.8728	
	ppm	*S/N* at LoQ
LoD	12.8	
LoQ	73.7 39.0	
Isopropanol		
Concentration (ppm)	*Areas*	
5.0405	35	
10.0809	58	
20.1618	109	
50.4045	230	
126.0114	561	
252.0227	1078	
Slope	4.2219	
Residual standard deviation (a)	6.9374	
	ppm	*S/N* at LoQ
LoD	5.4	
LoQ	46.1 16.4	

Table 4: Preparation for linearity solutions

Level (%)	*mL of Solution-A*	*Diluted to mL*	*Concentration (ppm)*		
			Ethanol	*Methanol*	*Isopropanol*
LoQ	0.5	25	50.0	30.08	50.40
25	1.0	20	124.9	75.22	126.01
50	2.0	20	249.9	150.44	252.02
75	3.0	20	374.9	225.67	378.03
100	10.0	50	499.9	300.89	504.04
125	5.0	20	624.9	376.12	630.05
150	6.0	20	749.9	451.34	756.06

Precision

The analytical precision of the method is the repeatability of the results obtained from a homogenous sample with different sets of sample preparations.

System Precision

The precision of the system expresses the instrument accuracy over a short period of time when injected with replicate injections of standard. The %RSD for area of ethanol, methanol, and isopropanol as shown in Table 8 proves the precision of standard injections.

Preparation of standard

Accurately weighed and transferred 1008.6 mg of ethanol, 603.0 mg of methanol and 1003.0 mg of isopropanol in individual 20 mL of volumetric flask which contains 10 mL of DMF. Diluted the solution up to mark with DMF and mixed well.

Transferred 5.0 mL of individual stock solution into a common 100 mL volumetric flask which contains 10 mL of DMF. Diluted the solution with DMF and mixed well.

Transferred 10.0 mL of common stock solution into a common 50 mL volumetric flask which contains 10 mL of DMF. Diluted the solution with DMF and mixed well (Concentration of Ethanol – 504.3 ppm. Methanol – 301.5 ppm and Isopropanol – 501.5 ppm).

The %RSD for area of solvent analyte peaks were determined as 2.7, 2.5 and 2.7 for ethanol, methanol and isopropanol respectively which is less than 15.0% of acceptance criteria as mentioned in Table 8. Hence, it ensures the precision of the instrument with consecutive standard injections.

LoQ Precision

The predicted LoQ level for all solvents were evaluated for precision.

LoQ solution preparation

Weighed 1000.2 mg of ethanol, 601.2 mg of methanol, and 1004.2 mg of isopropanol and transferred to an individual 20 mL volumetric flask which contains 10 mL of DMF. Made

Table 5: Linearity results of ethanol

Linearity level (%)	*Concentration (ppm)*	*Areas*
LoQ	50.0	196
25	125.0	528
50	250.1	1019
75	375.1	1578
100	500.2	2135
125	625.3	2469
150	750.3	3076
Slope		4.0661
Correlation Coefficient (R)		0.9987
Y-Intercept		16.9627
Y-Int Bias at 100%		0.8

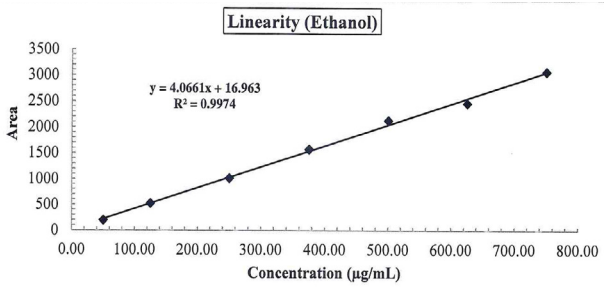


Fig. 4: Linearity graph for ethanol

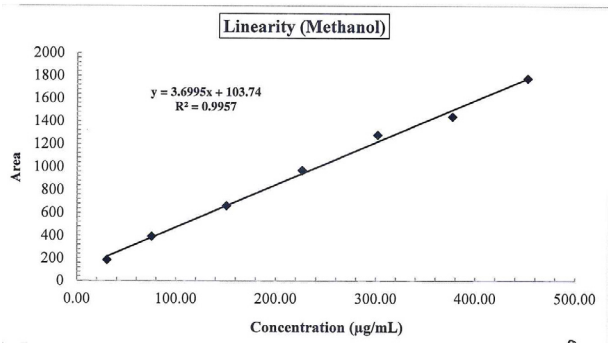


Fig. 5: Linearity graph for methanol

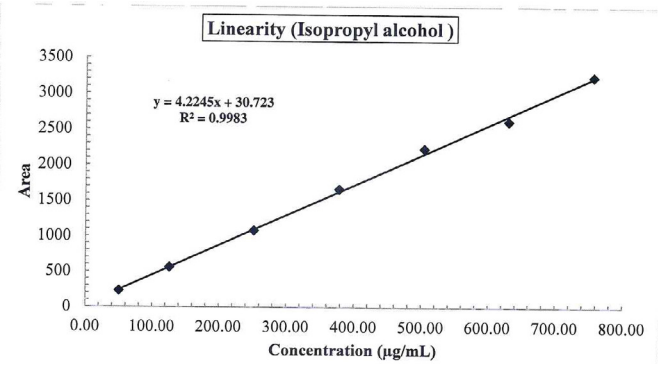


Fig. 6: Linearity graph for isopropanol

Table 6: Linearity results of methanol

Linearity level (%)	*Concentration (ppm)*	*Areas*
LOQ	30.1	184
25	75.3	392
50	150.7	659
75	226.1	968
100	301.4	1276
125	376.8	1438
150	452.2	1776
Slope		3.6995
Correlation Coefficient (R)		0.9978
Y-Intercept		103.7368
Y-Int Bias at 100%		8.1

up the solutions up to mark with DMF and mixed well.
1.2 mL of ethanol stock, 3.0 mL of methanol stock and 0.8 mL of isopropanol stock solution were transferred into individual 10 mL volumetric flasks which contain 2 mL of DMF. Made up the solutions to mark with DMF and mixed well.
In 1.0 mL of the above individual stock solutions were transferred into a common 250 mL volumetric flask that contains 10 mL of DMF. Made up the solution up to mark with DMF and mixed well.
(Concentration of Ethanol – 23.98 ppm. Methanol – 36.06 ppm and Isopropanol – 16.05 ppm).
The %RSD for area of solvent analyte peaks in the LoQ level is less than 15.0% as mentioned in Table 9. It ensures the capability of an analytical method for precision at a low concentration for all solvents. Hence, the predicted LoQ level is precise.

Method Precision

Precision of analytical methods has been established by the repeatability of preparation and analysis of six samples by spiking solvents at 100% specification level.

Table 7: Linearity results of isopropanol

Linearity level (%)	*Concentration (ppm)*	*Areas*
LOQ	50.4	230
25	126.0	561
50	252.0	1078
75	378.0	1661
100	504.0	2228
125	630.0	2613
150	756.0	3236
Slope		4.2245
Correlation Coefficient (R)		0.9991
Y-Intercept		30.7234
Y-Int Bias at 100%		1.4

Table 8: System precision results

Peak areas of analytes for replicated injection of standard solutions			
Injection number	*Methanol*	*Isopropanol*	*Ethanol*
1	1232	2198	2190
2	1191	2116	2108
3	1211	2164	2155
4	1260	2252	2244
5	1195	2116	2112
6	1180	2104	2099
Average*	1212 ± 29.857	2158 ± 58.164	2151 ± 57.025
%RSD	2.5	2.7	2.7
Specification	Not More Than 15.0%		

*Data are presented in as mean ± Standard Deviation with n = 6

Preparation of spike sample

Accurately weighed and transferred six samples (0.5013, 0.5020, 0.5018, 0.05012, 0.5006 and 0.5027 g) into individual 20-mL headspace vials. Added 5.0 mL of standard solution (as prepared under system precision), immediately sealed with septum, crimped cap and mixed gently.
Calculated the ppm and %RSD of each solvent as mentioned in methodology. Table 10 shows the %RSD of ethanol, methanol and isopropanol was determined below 10%. Thus, it ensures the precision of repeatability of analysis and produces precise results.

Accuracy

The accuracy or recovery of an analytical method is the closeness of the test results obtained by that method to the theoretical value. The accuracy (recovery) study has been performed by spiking the solvents solution into sample solution at different concentration levels such as LoQ, 50, 100 and 150 % of specification level; each in triplicate preparations. The results of recovery study

Table 9: LoQ results

Peak Area of analytes for replicate injection of standard solution						
Injection number	*Ethanol (23.98 ppm)*		*Methanol (36.06 ppm)*		*Isopropanol (16.05 ppm)*	
	Area	*S/N*	*Area*	*S/N*	*Area*	*S/N*
1	89	65.2	157	95.5	66	45.7
2	93	66.3	163	95.9	70	45.2
3	97	65.4	184	97.9	73	46.9
4	91	67.2	160	98.6	69	47.6
5	97	68.4	135	96.4	72	46.8
6	91	62.5	158	97.5	69	47.8
Average*	93 ± 3.346	65.8 ± 2.018	160 ± 15.630	97.0 ± 1.219	70 ± 2.483	46.7 ± 1.030
%RSD	3.7	3.1	9.8	1.3	6.7	2.2
Specification	NMT 15.0%					

*Data are presented in as mean ± Standard Deviation with n=6

Table 10: Method precision results

Method precision	*Methanol (ppm)*	*Isopropanol (ppm)*	*Ethanol (ppm)*
Sample-1	2220	4127	3913
Sample-2	2824	5297	4993
Sample-3	2640	4922	4631
Sample-4	2700	5072	4760
Sample-5	2656	4920	4642
Sample-6	2595	4758	4506
Average*	2606 ± 204.515	4849 ± 397.584	4574 ± 363.201
%RSD	7.8	8.2	7.9
Acceptance criteria	NMT 10%		

*Data are presented in as mean ± Standard Deviation with n = 6

Table 11: Methanol recovery results

%Level	*Solvent added (ppm)*	*Solvent recovered (ppm)*	*Recovery (%)*	**Average recovery (%)*	*%RSD*
		314.0	81.3		
LoQ	386.0	321.0	83.2	81.3 ± 1.950	2.4
		306.0	79.3		
		1403.0	93.1		
50	1507.0	1389.0	92.1	92.1 ± 1.414	1.1
		1374.0	91.1		
	3015.0	2678.0	88.8		
100	2580.0	2630.0	87.2	87.2 ± 1.600	1.8
	85.6				
		4283.0	94.7		
150	4522.0	3837.0	84.9	92.7 ± 7.058	7.6
		4459.0	98.6		
Overall Average (excluding LoQ level)				90.7 ± 3.017	5.0

*Data are presented in as mean ± Standard Deviation with n=3

Table 12: Ethanol recovery results

%Level	*Solvent added (ppm)*	*Solvent recovered (ppm)*	*Recovery (%)*	**Average recovery (%)*	*%RSD*
		218.0	90.1		
LoQ	242.0	222.0	92.0	90.4±1.473	1.6
		215.0	89.1		
		2532.0	100.5		
50	2519.0	2497.0	99.1	99.3±1.113	1.1
		2476.0	98.3		
		4771.0	94.7		
100	5038.0	4647.0	92.2	92.3±2.400	2.6
		4529.0	89.9		
		7595.0	100.5		
150	7558.0	6689.0	88.5	98.3±8.906	9.1
		8005.0	105.9		
Overall average (excluding LoQ level)				96.6±3.785	5.9

*Data are presented in as mean ± Standard Deviation with n=3

Table 13: Isopropanol recovery results

%Level	*Solvent added (ppm)*	*Solvent recovered (ppm)*	*Recovery (%)*	**Average recovery (%)*	*%RSD*
		146.0	91.2		
LOQ	160.0	151.0	94.1	91.2±2.900	3.2
		142.0	88.3		
		2644.0	105.5		
50	2507.0	2604.0	103.9	104.1±1.311	1.3
		2581.0	102.9		
		4997.0	99.7		
100	5014.0	4839.0	96.5	96.6±3.00	3.1
		4697.0	93.7		
		7919.0	105.3		
150	7521.0	6918.0	92.0	102.8±9.834	9.6
		8365.0	111.2		
Overall average (excluding LoQ level)				101.2±4.007	6.2

*Data are presented in as mean ± Standard Deviation with n = 3

obtained well within the acceptance criteria of 80.0 to 120.0% with %RSD of less than 15.0 as presented in Table 11 to 13. Recovery of analyte at different concentration ensures the accuracy of the method and as it presented in Table 11 to 13, each solvent provides the accuracy of recovered solvents. Hence the method is accurate for the quantification of residual solvents in phenylephrine hydrochloride USP.

Conclusion

In this research paper, it shows the method was successfully validated as per ICH Q2R(2) guidelines for method validation and obtained precise, linear and accurate results for the determination of residual solvent in phenylephrine hydrochloride USP. The method has the capability to detect the solvents at very low levels i.e. 7.7, 12.8 and 5.4 ppm for ethanol, methanol, isopropanol, respectively and quantify precisely at LOQ level (24.0, 36.1 and 16.1 ppm) with %RSD of 3.7, 9.8 and 6.7%. Moreover, the overall average recovery was determined as 90.7, 96.6, 101.2%, respective solvents. The data shows the analytical method's potential for the quantification of solvents by HS-GC in certain pharmaceutical dosage forms such as soft gel

capsules, oral solutions etc., which contains the usage of solvents in the manufacturing process. This analytical method is quite easy, reliable, cost-effective, suitable for the analysis of residual solvents in phenylephrine hydrochloride USP and produces consistent results in quality control environment.

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