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Research Article

An Effective Quantitative Gas Chromatography-Head Space Method Development And Validation For Isopropyl Alcohol Content In Mesalamine Prolonged Release Tablets

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ABSTRACT

This study developed and validated a straightforward, accurate, and sensitive head space-gas chromatography method for measuring the content of isopropyl alcohol in mesalamine prolonged-release tablets. The method uses Agilent Head space-gas chromatography, which has a flame ionization detector, capillary mid-polar stationary phase [DB-624 6% cyanopropyl, 94% polydimethylsiloxane (30 m*0.53 mm, 3µm)] with nitrogen as the carrier gas, and a linear velocity flow rate of 27 ml/min with a 1:5 spilt ratio and an injector temperature of 150 °C. The experiment ran for a total of twelve minutes, and the isopropyl alcohol retention time (RT) was 4.010 min. The developed method was validated according to the current International Conference on Harmonization (ICH) Q2R1 validation guidelines and Q3C standards for residual solvents. This method shows that it is specific, linear, precise, sensitive, rugged, reproducible, and effectively applied for the quantification of isopropyl alcohol in mesalamine prolonged-release tablets and quality control practices.

INTRODUCTION

Mesalamine is a synthetic derivative of salicylic acid, it is chemically known as 5-Amino-2-Hydroxy benzoic acid and mesalazine with molecular formula C7H7NO3 and molecular weight 153.15g/mol its structure is represented in Fig 1. A. This is the first-line medication to treat ulcerative colitis. Usually used to induce or maintain remission of mildly to moderately active ulcerative colitis. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall in the liver and excreted by the kidney as N-Acetyl-5-amino salicylic acid [1-3]

Residual Solvents are the organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients in the preparation of drug products. These solvents

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are not completely removed by practical manufacturing techniques (usually under increased temperature or decreased temperature) in use, even after such process some solvents still remain in small quantities. These quantities of organic solvents are commonly known as "Organic Volatile Impurities (OVIs) or Residual Solvents (RS). These solvents have no therapeutic value and are toxic to the human body if intake goes beyond the limit. Quantification of residual solvents is an integral part of quality control in pharmaceuticals. Different analytical techniques are available for the estimation of residual solvents in pharmaceuticals and other products including, Loss on drying (LOD), Thermal gravimetric analysis (TGA), Different scanning colorimetry (DSC), Different thermal analysis (DTA), Thermal desorption (TD), Chemical sensors and some spectrometric and spectroscopic procedures. However, these methods have low sensitivity, but gas chromatography-based test procedures are the most popular and are chemically specific for residual solvents [4-6]. According to ICH guidelines residual solvents have been classified into four types based on their toxicity profile. Their acceptable limits are listed in Table 1[7].

Table 1: Limit of residual solvents and toxicity criteria as per ICH (ICH Q3C)

Sr. No	Class	Solvent	Limit
1	Class-1[(a)]	Benzene	2
2		Carbon tetrachloride	4
3		1,2-Dichloroethane	5
4		1,1-Dichloroethane	8
5		1,1,1-Trichloroethane	1500
6	Class-2[(b)]	Acetonitrile	410
7		Methanol	3000
8		Chloroform	60
9		Cyclohexane	3880
10		Chlorobenzene	360
11		Hexane	290
12		Formamide	220
13		Pyridine	200
14		Toluene	890
15		Nitromethane	50
16		Sulfolane	160
17		Dichloromethane	600
18		N,N Dimethylacetamide	1090
19		Acetic acid	5000
20		2-Propanol	5000
21		Acetone	5000
22		Anisole	5000
23		2-Butanol	5000

24	Class-3[(c)]	Ethyl acetate	5000
25		Formic acid	5000
26		Heptane	5000
27		Butyl acetate	5000
28		Dimethyl sulfoxide	5000
29		Pentane	5000
30		Ethyl ether	5000
31		Isopropyl acetate	5000
32		Propyl acetate	5000

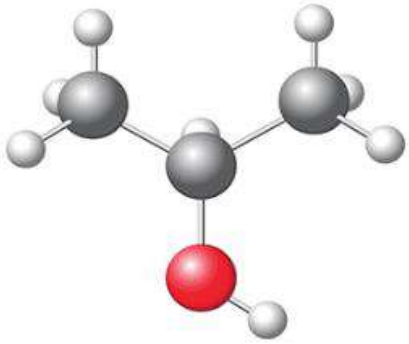
(a):Solvents to be avoided. (b):Solvents to be limited. (c):Solvents with low toxic potential.

Isopropyl alcohol (Propan-2-ol):

Isopropyl alcohol (Fig.1.B) is categorized as a Class –3, Solvents with low toxic potential. It is a colorless, flammable organic solvent with a pungent alcoholic odor. A molecular formula C3H8O, Boling point is 82.3℃ From the literature, several analytical techniques are accessible in mesalamine quantification like UV spectroscopic methods [8], RP-HPLC [9], Stability indicating RP-HPLC [10], HPLC-ESI-MS/MS method [11], RP-UPLC [12], RP-UHPLC [13]. Therefore, in this research, we strive to develop a simple, sensitiveand rapid method for quantification of isopropyl alcohol content in mesalamine prolonged-release tablets using a gas chromatographic method. Head Space-Gas chromatography was selected for initial separations from the knowledge of the properties of the compound.

Fig.1: Structure of Mesalamine (A) and Isopropyl alcohol (B)

A



B

Initial chromatographic conditions:

Column, oven temperature, Sample line temperature, pressurize gas pressure, equilibrating time, pressuring time, pressure equilibration time, injection time, needle flush time, injection mode, flow control mode, pressure, total flow, column flow, purge flow, split ratio, oven program, makeup gas, make up flow, hydrogen flow and airflow. Above mentioned parameters needed to be tuned based on the physiochemical properties of the sample. After careful optimization of the method for the quantification of "Isopropyl alcohol". The optimized method is to be validated as per ICH guidelines.

MATERIALS AND METHODS

Reagents and chemicals used:

Solvents used were of ≥ 99.8% purity N, N Dimethyl formamide and Isopropyl alcohol were purchased from Merck Life Sciences Private Limited; PADM Laboratories provided Mesalamine prolonged-release tablets.

Instruments and apparatus:

Chromatographic elution was carried out in Gas chromatography (Agilent technologies 6890N Series) with a Flame ionization detector (FID) and Headspace sampler (Agilent technologies G18888 Series), Separation was achieved using a DB-624 6% cyanopropyl, 94% polydimethylsiloxane Stationary phase (30 m*0.53 mm, 3µm). Mettler Toledo Analytical balance, Microbalance, and Vortex Genie 2 were used for sample preparation.

Chromatographic conditions:

Instrument	Gas chromatography equipped with an FID Detector and headspace spilt mode injector
Stationary phase	30mt×0.53mm ID×3µm, DB-624 capillary column
Column temperature	50°C (hold for 6 mins), then raised to 230°C at the rate of 60°C per min and hold that temperature for 3 min. Total run time is 9 mins.
Injector temperature	260°C
Carrier gas	Nitrogen @ 20.1Kpa pressure at linear velocity
Total flow	27ml/min
Column flow	4.01ml/min
Purge flow	3ml/min
Split ratio	1:5
Head space Parameters	
Oven temperature	90
Loop temperature	150
Transfer line temperature	150
GC Cycle time	25mins
Vial equilibration time	5mins
Pressurizing time	1min
Loop equilibration time	0.1 min
Injection time	1min
Shake	Low

Solutions preparation:

Preparation of Blank solution:

Transferred 5 ml of N, N Dimethylformamide into a 20ml GC Headspace Vial and immediately sealed the Vial.

Diluent:

N, N Dimethyl formamide

Preparation of Standard stock solution:

Weighed accurately about 510.0 mg of Isopropyl alcohol WS into a 50ml volumetric flask containing 25 ml of diluent and shake well then diluted up to the mark with diluent.

Preparation of Standard solution:

Taken 1 ml of the standard stock solution into a 50 ml volumetric flask containing 25 ml of diluent and shake well then diluted up to the mark with diluent, and transferred 1 ml of the above solution into 20 ml GC Headspace vial and immediately sealed using a rubber septa and metallic ring closure.

Preparation of Sample solution:

Weighed accurately and transferred 200 mg of sample into 20 ml of GC Headspace vial and added 5 ml of diluent immediately sealed the vial, vortex for 5 mins.

METHOD DEVELOPMENT:

Method development was carried out through a series of trials by changing various stationary phases and diluents based on their physiochemical properties of analyte that was optimized by final trial by using a DB-624 mid-polar stationary phase with composition of 6% cyanopropyl, 94% polydimethylsiloxane (30mt ×0.53mm, 3µm) and N, N Dimethyl formamide used as a diluent. As stated in the limits of ICH, all the parameters were optimized by injecting blank, standard, and sample

solutions into the optimized chromatographic conditions. (Refer supporting info) The retention of diluent (N, N Dimethylformamide) was 8.82mins as shown in Figure 2, the retention time of standard was observed as 4.02 as shown in Figure 2 and the Retention time of sample solution was observed at 3.99 as shown in Figure 2.

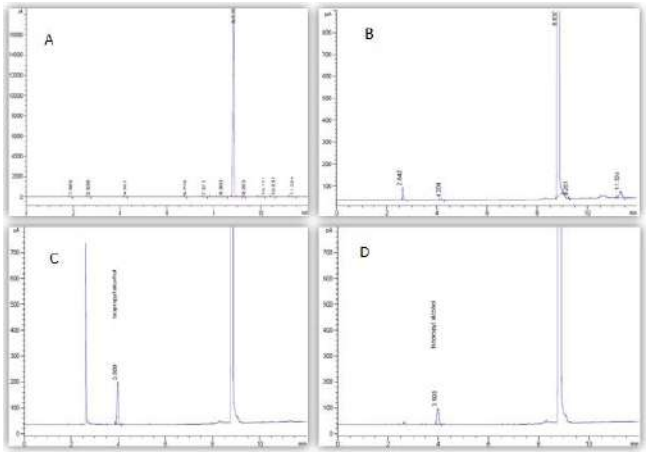


Fig.2: Representative Chromatograms for blank (A), Placebo (B), Standard Solution (C) and Sample Solution (D).

Method validation:

Specificity

Specificity of the method The ability of the method to measure the analyte in the presence of compounds such as process impurities, degradation impurities, and matrix components, by comparing the chromatograms of blank, placebo, standard, sample, and spiked sample solution. Fig.2 shows the typical chromatograms of blank, placebo, standard, and spiked sample solutions. Under the optimized chromatographic conditions the typical retention time of isopropyl alcohol was 3.98. There is no significant interference was observed due to blank, placebo, and other unknown peaks at the retention time of isopropyl alcohol, the resolution between isopropyl alcohol and closet impurity peak in specificity solution is 14.26. Based on the above results, the method is specific.

System suitability

Injected the blank and standard solution (six replicates) recorded the plate count of isopropyl alcohol from the standard injection and calculated the % RSD for the peak response of isopropyl alcohol from the six replicate standard injections. The theoretical plate number for the isopropyl alcohol peak in the standard solution was found 17580 and the % RSD for the peak areas of isopropyl alcohol calculated on six replicates of the standard solution is 1.01% (Table 2).

Table 2: System suitability of six replicated standard injections by optimized method

Standards	Area of Isopropyl alcohol peak	Retention Time of Isopropyl alcohol
Standard-1	732.030	3.991
Standard-2	734.484	3.980
Standard-3	744.656	3.981
Standard-4	734.137	3.981
Standard-5	728.093	3.979
Standard-6	746.957	3.982
Average	736.726	3.982
Standard deviation	7.428	0.004
% RSD	1.01	0.10

Precision

Precision was considered at three levels, repeatability, intermediate, and reproductively precision.

System precision

To determine the method precision six replicate injections of the standard solution will be made by the optimized method and the standard deviation and relative standard deviation (% RSD) of the six replicate injections will be calculated and reported then %RSD is not more than 15%. The % RSD of method precision was 1.01. As depicted in Table 2, hence the method was deemed suitable and precise.

Method precision

Method repeatability will be performed by injecting one unspiked and six spiked sample preparations. The % RSD for isopropyl alcohol content from the six sample preparations should be now more than 15% and the results are found to be 10.43%. The values are displayed in the table 3.

Intermediate precision

Intermediate precision is the degree of reproducibility of the test results attained same sample analysis and the method has been studied by evaluating the variations from the analyst and different stationary phases. It will be performed by one unspiked and six spiked sample preparations. Calculate the relative standard deviation peak response of six replicate injections should be not more than 15% and the values are displayed in table 4.

Table 3: Results of method precision (In ppm) *ppm-Parts per million

Spiked Sample preparation	Spiked Sample area	(Sample-Standard Average) area	Results in ppm
1	1230.212	493.486	3041.37
2	1105.750	369.024	2510.41
3	1292.082	555.356	3376.79
4	1197.621	460.895	2796.93
5	1254.263	517.537	3224.13
6	1212.727	476.001	2896.93
Average	NA	NA	2974.43
SD			310.339
%RSD			10.43

Table 4: Results of Intermediate precision (In ppm)

Spiked Sample preparation	Spiked Sample area	(Sample-Standard Average) area	Results
1	1314.121	561.870	3527.46
2	1321.634	569.383	3557.53
3	1237.772	485.521	3058.08
4	1222.903	470.652	2963.87
5	1190.588	438.337	2885.99
6	1215.640	463.389	3006.52
Average	NA	NA	3166.58
SD			296.746
%RSD			9.37

Detection Limit (DL) and Quantitation Limit (QL)

Instrumental and statistical approaches were used to determine the LOD and LOQ. The limits of detection (LOD) and quantification (LOQ) are identified by the detectors for the instrument approach. LOD and LOQ have been established by three injections of LOD levels and six injections by LOQ level. The concentration and signal-to-noise ratio was established in Table 5.

Table 5: the values for the LOD and LOQ

Name of the parameter	Concentration	S/N Ratio

Limit of detection	125ppm	8.1980
Limit of quantification	400ppm	14.8044

Linearity and Range

The linearity of an analytical procedure is its ability (within a given range) to obtain test results that are directly (i.e., after mathematical transformation) proportional to the concentration (amount) of analyte in the sample. Demonstrated the linearity parameter of the analytical method from the range 50% to 150% of the working concentration of the method by covering three different concentrations and drown a plot between concentration Vs average area response of isopropyl alcohol linearity level solutions.

From the statistical analysis, correlation coefficient, and regression equations, linearity is known as shown in Table 6 and the linearity graph was shown in figure 3. The isopropyl alcohol correlation coefficient values were noted to be higher than 0.9996 and the calibration curve was linear within the linear range.

Table 6: Results of Linearity and Range

LinearityLevel (%)	Concentration of Isopropyl Alcohol (In ppm)	Average Area of Isopropyl alcohol peak
50%	2498.6489	392.480
75%	3747.9733	608.294
100%	4997.2977	815.560
125%	6246.6221	1061.755
150%	7495.9466	1275.823
Correlation coefficient (r)		0.9996
Slope		0.1777
Intercept		-57.2764
Regression Coefficient (R^2)		0.9993
%Relative y- intercept		0.9996

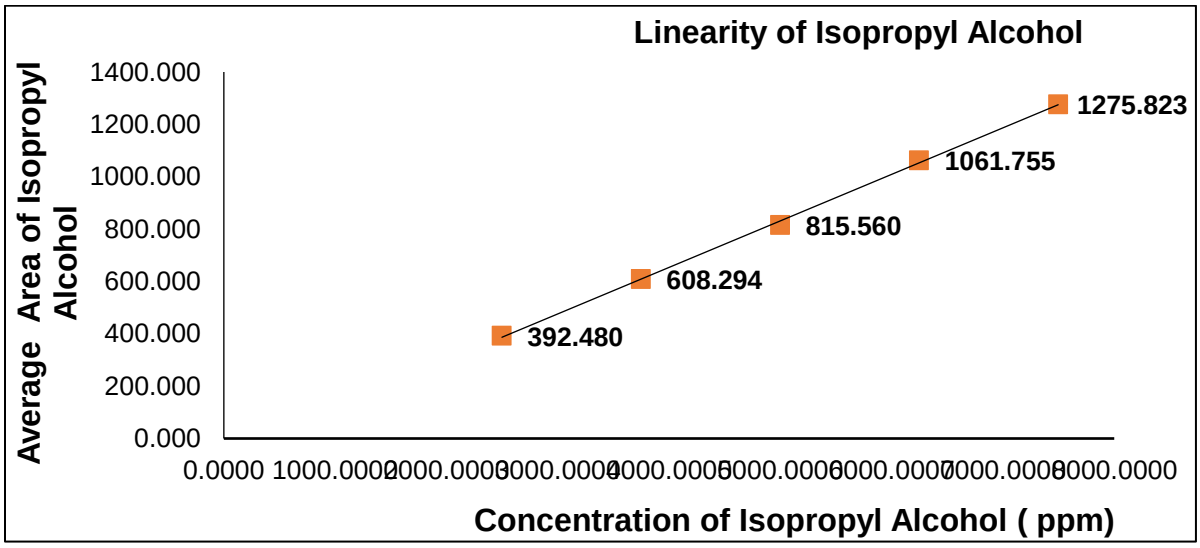


Fig 3: Linearity graph of Isopropyl alcohol

Accuracy (Recovery)

The accuracy of an analytical method is the closeness of the sample results obtained from the method to the truevalue. Accuracy may often be expressed as the percent of recovery by the assay of known added amounts of analyte to the matrix. Accuracy is a measure of the exactness of the analytical method. Accuracy will be performed from the range of QL to 150% of the specification level of isopropyl alcohol. Recoveries of 50%,

100%, and 150% were performed by mixing known amounts of standard drug solution, and the results are presented in Table 7. From the accuracy data, the %recovery of residual solvents was found within the limits and the %RSD for the area did not exceed 10.0 for isopropyl alcohol. The outcomes show that the strategy achieves a satisfactory degree of accuracy.

Table 7: Results of accuracy for Isopropyl alcohol

Accuracy solution	Actual amount of Isopropyl Alcohol WS added (mg/mL)	Amount of Isopropyl Alcohol found (mg/mL)	% Recovery	Mean % Recovery	% RSD
Level-1 (QL)	0.0004	0.0003	75.0	75.1	0.15
Level-2 (QL)	0.0004	0.0003	75.0		
Level-3 (QL)	0.0004	0.0003	75.2		
Level-1 (50%)	0.0025	0.0026	104.0	102.7	2.25
Level-2 (50%)	0.0025	0.0026	104.0		
Level-3 (50%)	0.0025	0.0025	100.0		
Level-1 (100%)	0.0050	0.0050	100.0	101.3	1.14
Level-2 (100%)	0.0050	0.0051	102.0		
Level-3 (100%)	0.0050	0.0051	102.0		
Level-1 (150%)	0.0075	0.0076	101.3	101.8	0.79
Level-2 (150%)	0.0075	0.0076	101.3		
Level-3 (150%)	0.0075	0.0077	102.7		
Overall % recovery	101.9				
SD	1.474				
Overall % RSD	1.45				

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness of the method was evaluated by checking the system suitability parameters by deliberately varying the chromatographic conditions such as setting Oven Temperature 86℃ and 94℃ instead of 90℃, the cumulative % RSD for isopropyl alcohol met to the acceptance criteria that are below 15% and the values are depicted in table 8 then Figure 4 shows the typical chromatogram of robustness of oven temperature. Optimal column flow was 4.01ml/min is changed to 3.8ml/min and 4.2ml/min respectively the consequence of the evaluation was good and the robustness of column flow chromatograms represented in figure 5 then %RSD for area of isopropyl alcohol below 15% and the values are summarized in table 9.

Table 8: System suitability for change in initial oven temperature (℃)

Name of the solution	Area condition (90^0)		Lower condition (86^0)		Higher condition (94^0)	
	Area	RT	Area	RT	Area	RT
Standard-1	739.863	3.995	649.914	3.999	820.098	4.003
Standard-2	754.546	3.999	642.093	4.000	751.201	4.002
Standard-3	752.674	3.999	648.405	3.997	828.097	4.003
Standard-4	751.111	3.999	667.260	4.001	844.032	4.003
Standard-5	773.874	4.000	672.010	3.998	619.936	4.001
Standard-6	778.378	3.999	665.537	4.000	875.433	4.002

Average	758.408	3.999	657.537	3.999	789.800	4.002
Standard deviation	14.717	0.002	12.231	0.001	92.739	0.001
% RSD	1.94	0.05	1.86	0.03	11.74	0.02

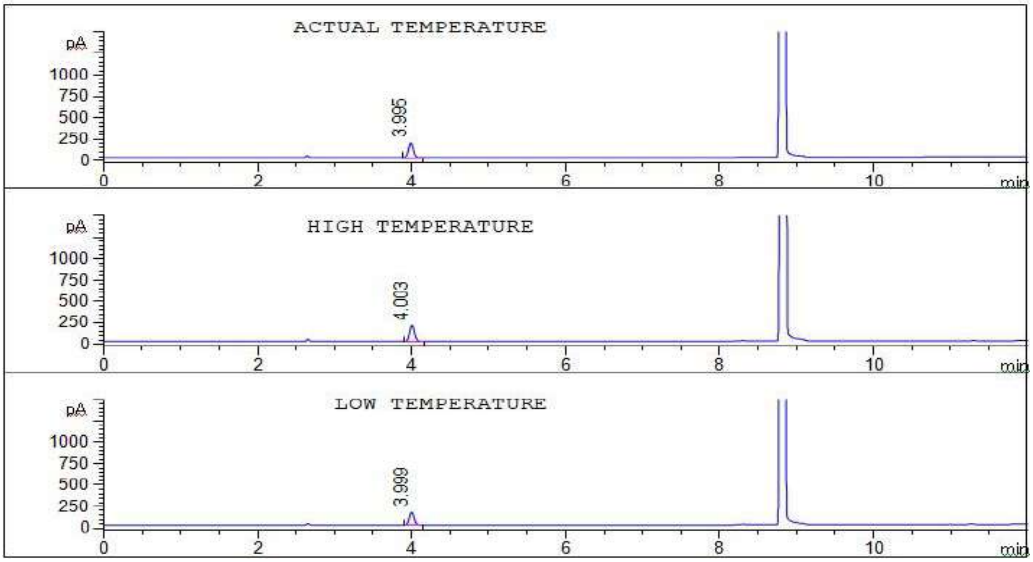


Figure 5: Representative chromatogram for Robustness of initial temperature (℃)

Table 9: System suitability for column flow (ml/min)

Name of the solution	Area condition (4.01ml/min)		Lower condition (3.8 mL/min)		Higher condition (4.2 mL/ min)	
	Area	RT	Area	RT	Area	RT
Standard-1	770.899	4.010	725.730	4.212	728.149	3.784
Standard-2	804.558	4.011	721.275	4.214	723.701	3.785
Standard-3	810.146	4.014	708.058	4.214	746.496	3.784
Standard-4	709.333	4.012	721.538	4.214	722.358	3.785
Standard-5	710.971	4.012	728.736	4.223	747.093	3.786
Standard-6	715.312	4.012	722.253	4.217	748.803	3.784
Average	753.537	4.012	721.265	4.216	736.100	3.785
Standard deviation	47.615	0.001	7.088	0.004	12.618	0.001
% RSD	6.32	0.02	0.98	0.09	1.71	0.03

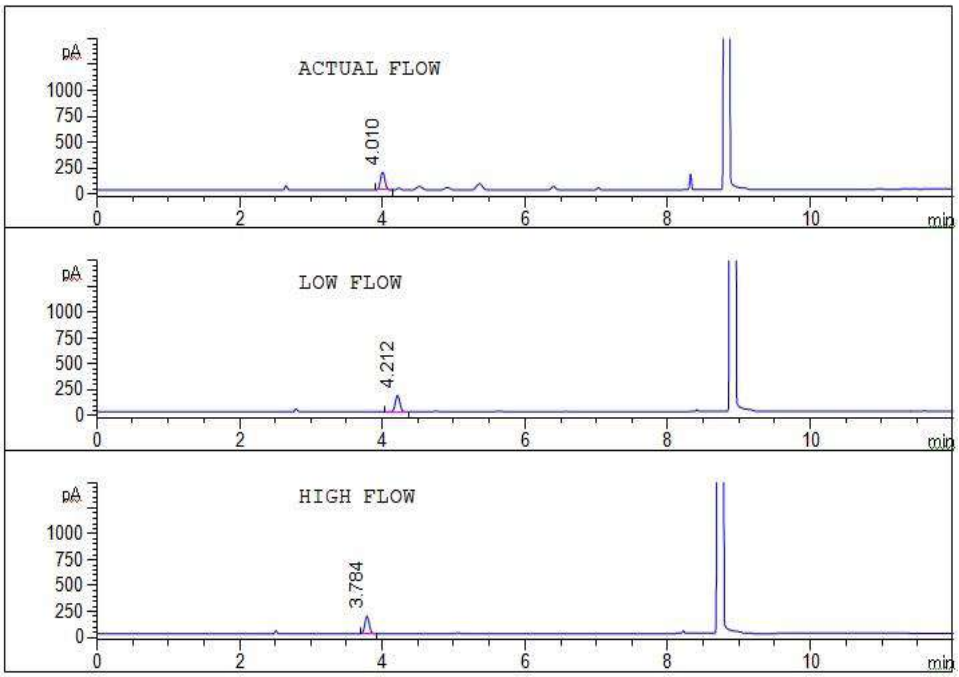


Figure 6: Typical Chromatogram for Robustness of column flow

CONCLUSION

The newly developed HS-GC-FID method underwent a validation successfully according to ICH Guidelines and was demonstrated to be specific, linear, precise, accurate, and robust for the estimation of isopropyl alcohol levels in mesalamine prolonged-release tablets. Therefore, this method is suitable for the conduct of testing in regulated quality control (QC) laboratories.

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