RESEARCH ARTICLE

Analytical Method Development and Validation Of Docusate Sodium to Determine Residual Solvent by Headspace Gas Chromatography

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Abstract

Introduction: The development of reliable analytical methods plays a crucial role in pharmaceutical quality control to ensure the safety, efficacy, and regulatory compliance of drug substances and products. Residual solvents are volatile organic impurities that may remain in active pharmaceutical ingredients (APIs) after manufacturing processes such as synthesis, purification, and crystallization. Since these solvents do not provide any therapeutic benefit and may pose toxicological risks when present above permissible limits, their determination is essential in pharmaceutical analysis. The International Council for Harmonisation (ICH) Q3C(R8) guideline classifies residual solvents based on their toxicity and establishes acceptable exposure limits.

Material and Methods: The present study was aimed at the development and validation of a rapid, sensitive, selective, and reliable Headspace Gas Chromatography coupled with Flame Ionization Detection (HS-GC-FID) method for the determination of residual solvents in Docusate Sodium API. The developed analytical method was validated in accordance with ICH Q2(R2) guidelines with respect to specificity, linearity, accuracy, precision, robustness, limit of detection (LOD), limit of quantitation (LOQ), and solution stability.

Result and Discussions: The validation results demonstrated that the method exhibited excellent specificity and good linearity with correlation coefficients greater than 0.99 for all selected residual solvents. Accuracy studies showed satisfactory recoveries within acceptable limits, while precision studies indicated %RSD values below 2.5%, confirming the reproducibility of the method.

Conclusion: The present study successfully developed and validated a reliable HS-GC-FID method for the determination of residual solvents in Docusate Sodium API.

Keywords: Docusate Sodium, residual solvents, HS-GC-FID, method validation, ICH Q3C(R8).

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Introduction

Analytical method development is an essential component of pharmaceutical research that involves the systematic design and validation of analytical procedures for the accurate identification and quantification of drug substances, impurities, and degradation products.[1,2] In the pharmaceutical industry, reliable analytical methods are crucial for quality control, regulatory compliance, stability studies, and ensuring the safety and efficacy of pharmaceutical products. Therefore, robust, precise, sensitive, and reproducible analytical methods play a vital role throughout the drug development and manufacturing process.[3] Residual solvents are volatile organic impurities that may remain in pharmaceutical products after synthesis, purification, or manufacturing processes. Since they do not provide any therapeutic benefit and may cause toxic effects even at low concentrations, their determination is essential for ensuring drug safety and quality. Residual solvents may also affect the physicochemical properties, stability, and overall performance of drug substances. Therefore, their control and quantification are important aspects of pharmaceutical quality control according to ICH guidelines.[4]

The International Council for Harmonisation (ICH) Q3C guideline provides a standardized approach for the control of residual solvents in pharmaceutical products based on their toxicity and potential risk to human health. According to the guideline, residual solvents are classified into three categories: Class 1 solvents, which should be avoided due to their carcinogenic or environmental hazards; Class 2 solvents, which are toxic and must be controlled within specified permitted daily exposure (PDE) limits; and Class 3 solvents, which possess low toxic potential and are considered less harmful under recommended concentration limits. This classification system helps ensure the safety, quality, and regulatory compliance of pharmaceutical products.[5,6]

Docusate Sodium is an anionic surfactant commonly used as a stool softener laxative and is classified as a BCS Class III drug with high solubility and low permeability. It acts by reducing the surface tension of stool, allowing water and lipids to penetrate and soften fecal matter.[7] During its synthesis and purification, solvents such as methanol and

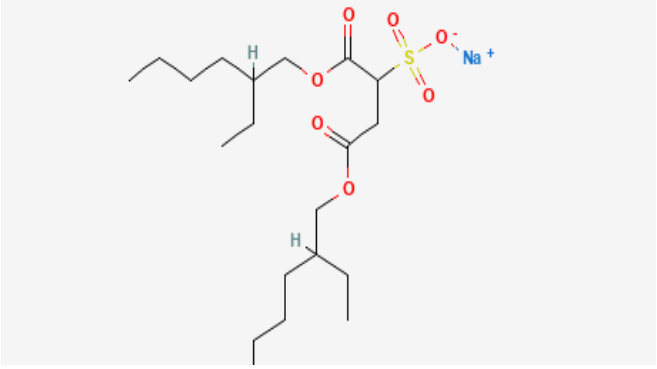

Fig 1: Structure of Docusate Sodium[9]

ethanol are commonly used for crystallization; however, incomplete drying may lead to residual solvent retention in the API, making their determination important for quality and safety evaluation. [8]

Research Methodology

Material

Used chemicals were obtained from following supplier:
methanol, toluene, N-Methyl-2-Pyrilidone - Laxachem organics Pvt. Ltd.
Also, API Docusate sodium was obtained from Laxachem organic Pvt. Ltd.

Instrumentation

A Gas Chromatograph (Agilent technologies 8890 GC system) equipped with a flame ionization detector, a Headspace sampler (Agilent technologies 7697A HS) was used to load the sample. An analytical balance (Shimadzu AUW 220D) and micropipette (100 – 1000 µL) were used.

Chromatographic condition-

For the gas chromatographic analysis a DB-624 column (30 m length and 0.53 mm internal diameter 3.0 micro meter film thickness) was used. Nitrogen was used as a carrier gas. Flow rate was kept 5 mL/min. Split ratio was 10:01. Detector temp was 260°C Oven temp was Initial 40°C hold for 6mins.Ramp rate 10°/min raise temp. to 220°C hold for 5mins.

Development by new analytical method:

Preparations of solutions [10]

Preparation of methanol and toluene stock solution:

10mg methanol and 10mg toluene were accurately weighed and added into the headspace vial. 5ml of diluent (N-Methyl-2-pyrrolidone) was added into the same vial.

Preparation of peak identification solution:

10mg of solutions were accurately weighed and added into headspace vial. 5ml of diluent (N-Methyl-2-pyrrolidone) was added into the same vial.

Preparation of Standard Solution of Methanol and Toluene

Pipette out 1 ml of methanol and toluene stock solution into a 50 ml volumetric flask. Add 20 ml diluent, dissolve, and dilute to volume with diluent.

Preparation of Sample Solution

Accurately weigh about 0.5 g sample into a headspace vial, add 5 ml diluent.

Preparation of Spiked Sample Solution

Accurately weigh about 0.5 g sample into a headspace vial, add 5 ml of methanol and toluene standard solution.

Analytical Method Validation

The developed HS-GC-FID method was validated according to ICH Q2(R2) guidelines for specificity, LOD, LOQ, linearity, range, accuracy, precision, robustness, and system suitability. Specificity studies confirmed adequate separation of methanol and toluene without interference from diluent or sample matrix. The method showed good sensitivity with acceptable LOD and LOQ values. Excellent linearity was observed from LOQ to 150% concentration levels with satisfactory correlation coefficients. Accuracy studies demonstrated acceptable recoveries at different spiking levels, while precision studies showed %Relative Standard Deviation values within acceptable limits, confirming repeatability and reproducibility. Robustness studies indicated that small deliberate variations in chromatographic conditions did not significantly affect method performance. System suitability results confirmed satisfactory chromatographic efficiency and reliable performance of the developed method.[11-13]

Result and Discussion

System suitability

System suitability testing was performed to ensure the proper functioning and reliability of the analytical system under optimized chromatographic conditions throughout the study. Show in Table 1.

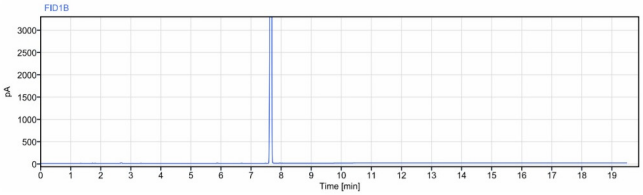

Fig 2: Chromatogram of Blank (NMP)

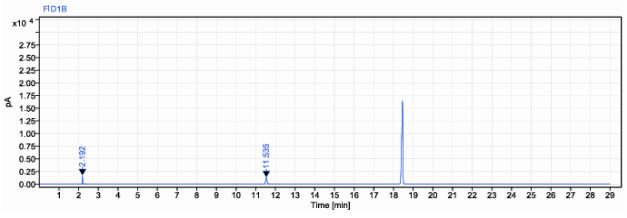

Fig 3: Chromatograph of optimized method

Table 1: System suitability

Sr. No	*Parameters*	*Methanol*	*Toluene*	*Acceptance criteria*
1	Mean RT	2.200	11.460	-
2	% RSD (RT)	0.00	0.00	NMT 1.0
3	Mean Area	484.845	285.038	-
4	% RSD (Area)	2.8	4.2	NMT 15.0

Linearity

The correlation coefficient for both analytes was found to be not less than 0.98, and residual values were within the acceptable limit of ±20%, confirming linearity of the method.

Observation

The R^2 value was found to be 0.9999 which is within the acceptable limits (Table 2).

Toluene

Observation

The R^2 value was found to be 0.9995 which is within the acceptable limits (Table 3).

Accuracy

Recovery values obtained at LOQ level were within 70–120%, while recovery values at 100% and 150% levels were within 80–120%. The %RSD of recovery values was within the acceptance limit of 15%. Formula: % Recovery = Amount recovered/Amount added ×100 (Table 4).

Precision

The %RSD for peak area and retention time was found within the acceptable limits.

Table 2: Linearity of methanol

Sr. No	*Linearity (PPM)*	*Peak area*
1	89.964	144.073
2	149.940	237.413
3	239.903	374.027
4	299.879	478.673
5	359.855	579.883
6	449.819	715.013
	$r^2 = 0.9999$	

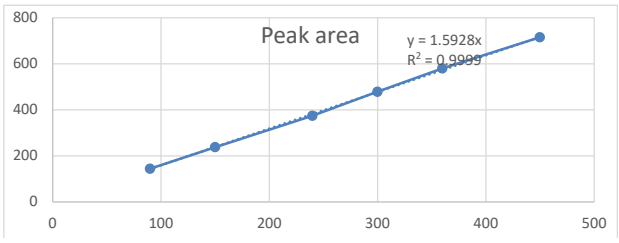

Fig 4: Calibration curve of methanol

Table 3: Linearity of Toluene

Sr. No	*Linearity (PPM)*	*Peak area*
1	26.507	79.88
2	44.178	130.883
3	70.685	219.54
4	88.356	253.997
5	106.027	322.84
6	132.534	399.823
	$r^2 = 0.9995$	

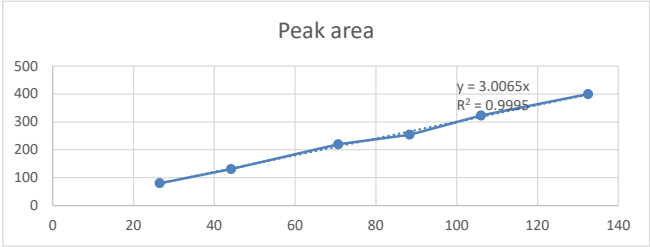

Fig 5: Calibration curve of toluene

Table 4: % Recovery of Methanol and Toluene

Sr. No	*Accuracy level*	*%Mean Recovery*	*SD*	*%RSD*
A)	*Methanol*			
1	LOQ (I)	106.5	2.2	2.1
2	100% (II)	101.9	2.4	2.4
3	150% (III)	102.2	0.7	0.7
4	Overall	103.6	2.8	2.7
B)	Toluene			
1	LOQ (I)	111.7	1.7	1.5
2	100% (II)	112.0	1.4	1.3
3	150% (III)	110.1	2.4	2.2
4	Overall	111.2	2.0	1.8

System Precision

Table 5: System Precision

Sr. No	*Parameters*	*Methanol*	*Toluene*	*Acceptance criteria*
1	Mean RT	2.237	11.526	-
2	% RSD	0.10	0.00	NMT 1.0
3	Mean Area	489.68	275.50	-
4	% RSD Area	1.16	1.69	NMT 15.0

Method Precision (Repeatability)

Table 6: Method Precision

Sr. No	*Parameters*	*Methanol*	*Toluene*	*Acceptance criteria*
1	Mean Area	532.17	298.22	-
2	SD	21.44	4.01	-
3	% RSD	4.03	1.34	NMT 15.0

Intermediate Precision:

Table 7: Intermediate Precision

Sr.No	*Parameters*	*Methanol*	*Toluene*	*Acceptance criteria*
1	Mean RT	2.236	11.525	-
2	% RSD	0.045	0.026	NMT 1.0
3	Mean Area	482.19	277.92	-
4	% RSD Area	2.94	3.72	NMT 15.0

Specificity

The results specificity showed no interfering peaks at the specific retention time of Docusate Sodium, confirming that the analytical response is attributed solely to the analyte. This clear resolution ensures that the method is highly selective and capable of providing accurate results without interference from the sample matrix or mobile phase.

Specificity of components

Table 8: Specificity

Sr. No	*Component*	*RT*	*Interference*
A)	Benzene		
1	Blank	-	Nil
2	Benzene	8.348	Nil
B)	Methanol		
1	Blank	-	Nil
2	Methanol	2.231	Nil
C)	Toluene		
1	Blank	-	Nil
2	Toluene	11.521	Nil

Table 9: Robustness

Sr.No	*Conditions Variation*	*Parameters*	*Methanol (%RSD)*	*Toluene (%RSD)*	*Acceptance Criteria*
1	Standard Condition	Area	1.2	1.8	NMT 15.0
2		RT	0.00	0.00	NMT 1.0
3	Flow Rate (5.1 ml/min)	Area	2.8	4.2	NMT 15.0
4		RT	0.00	0.00	NMT 1.0
5	Flow Rate (4.9 ml/min)	Area	1.1	1.4	NMT 15.0
6		RT	0.00	0.00	NMT 1.0
7	Detector Temperature (258°C)	Area	1.5	1.9	NMT 15.0
8		RT	0.00	0.00	NMT 1.0
9	Detector Temperature (262°C)	Area	1.9	2.5	NMT 15.0
10		RT	0.00	0.00	NMT 1.0
11	Injector Temp (218°C)	Area	1.3	1.8	NMT 15.0
12		RT	0.00	0.00	NMT 1.0
13	Injector Temp (222°C)	Area	1.7	2.3	NMT 15.0
14		RT	0.00	0.00	NMT 1.0

Table 10: LOD AND LOQ

Sr. No	*Parameters*	*Methanol*	*Toluene*
1	LOD Level (% of Standard)	10%	10%
2	Mean RT (min)	2.240	11.531
3	%RSD (RT)	0.000	0.007
4	%RSD (Area)	1.62	2.05
5	Mean S/N Ratio (LOD)	12.9598	3.4046
6	LOQ Level (% of Standard)	30%	30%
7	Mean S/N Ratio (LOQ)	45.7498	12.0998
8	%RSD at LOQ (Area)	0.98	1.34

Robustness

The results showed negligible changes in the measured parameters, with relative standard deviation (%RSD) values remaining well within acceptable limits. This confirms that the developed method is robust and maintains its performance and consistency despite minor fluctuations in analytical conditions (Table 9).

LOD & LOQ

LOD limit for S/N ratio should be not less than 3 and LOQ limit for S/N ratio should be not less than 10.
S/N Ratio (LOD)= 12.9598
S/N Ratio (LOQ= 45.7498 (Table 10).

Conclusion

The present study successfully developed and validated a reliable HS-GC-FID method for the determination of residual solvents in Docusate Sodium API. The method showed satisfactory specificity, accuracy, precision, linearity, sensitivity, and robustness in accordance with ICH guidelines. Efficient separation and quantification of methanol and toluene were achieved with minimal sample preparation and high reproducibility. The validated method is suitable for routine quality control, stability studies, and regulatory compliance monitoring, ensuring the safety, quality, and reliability of pharmaceutical products.

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