WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 6, 1188-1201. Research Article ISSN 2277–7105

RP-HPLC METHOD DEVELOPMENT AND METHOD VALIDATION FOR SIMULTANEOUS QUANTIFICATION OF DOMPERIDONE AND CINNARIZINE IN SOLID DOSAGE FORM

H. Durga Prasad*[1], Dr. K. Atchuta Kumar[2], Miss. N. Poojitha[3], Mrs. P. Prathyusha[4], Mrs. A. Kanaka Durga Valli[5]

[1*]Srinivasarao College of Pharmacy, P.M. Palem, Visakhapatnam-530041, Andhra Pradesh India.

[2,3,4,5]Srinivasarao College of Pharmacy, P.M. Palem, Visakhapatnam-530041, Andhra Pradesh India.

Article Received on 15 Feb. 2026,
Article Revised on 05 March 2026,
Article Published on 16 March 2026,

https://doi.org/10.5281/zenodo.19046877

***Corresponding Author**

H. Durga Prasad

Srinivasarao College of Pharmacy, P.M. Palem, Visakhapatnam-530041, Andhra Pradesh India.

How to cite this Article: H. Durga Prasad*[1], Dr. K. Atchuta Kumar[2], Miss. N. Poojitha[3], Mrs. P. Prathyusha[4], Mrs. A. Kanaka Durga Valli[5]. (2026). Rp-Hplc Method Development And Method Validation For Simultaneous Quantification of Domperidone and Cinnarizine In Solid Dosage Form. World Journal of Pharmaceutical Research, 15(6), 1188–1201.

ABSTRACT

Method development and validation is the process of developing and testing techniques for measuring the components of a product. It is a critical component of drug development and quality control. The main purpose is to guarantee that techniques for measuring drug identification, purity, potency, and stability are accurate, precise, and dependable. Analytical procedures are essential instruments for ensuring the safety, efficacy and quality of drugs during their development process. Using RP-HPLC, a simple and accurate technique for estimating Domperidone and Cinnarizine simultaneously was created. The peaks were well separated at 226nm in isocratic mode at 2.578 and 3.616 min retention times for Domperidone and Cinnarizine respectively at 1.2ml/min flow rate with Welchrom 250mm x 4.6mm, 5µm column for 20min. Orthophosphoric acid buffer: acetonoitrile (70:30) as mobile phase. The % Assay values for Domperidone and Cinnarizine were 99.76% and 99.85%, respectively. The linearity correlation coefficient was 0.9991 & 0.9992 for Domperidone and Cinnarizine respectively.

KEYWORDS: Domperidone, Cinnarizine, Method development and validation, ICH

guidelines, and RP-HPLC.

1. INTRODUCTION

1.1 DRUG PROFILE OF DOMPERIDONE

Domperidone is a selective dopamine receptor antagonist that promotes movement of the gastrointestinal tract and stimulates the release of prolactin that is utilized as an antiemetic. It serves as a valuable tool in researching dopaminergic pathways. Domperidone functions as an adjunct for delayed gastrointestinal emptying and as a stimulant of peristalsis. Its gastroprokinetic effects are attributed to its ability to block peripheral dopamine receptors. Domperidone improves gastric emptying by increasing esophageal and gastric peristalsis and decreasing esophageal sphincter pressure. Domperidone's efficacy as an antiemetic is due to its ability to inhibit dopamine receptors in the chemoreceptor trigger zone and in the stomach. It has a considerable affinity for D2 and D3 dopamine receptors in the chemoreceptor trigger zone, which is situated immediately outside the blood-brain barrier and regulates nausea and vomiting. Domperidone's IUPAC name is 5-chloro-1-{1-[3-(2-oxo-2, 3-dihydro-1H-1, 3-benzodiazol-1-yl) propyl] piperidin-4-yl}-2, 3-dihydro-1H-1, 3-benzodiazol-2-one. Its molecular weight is 425.91g/mol. The chemical formula of Domperidone is $C_{22}H_{24}ClN_5O_2$.[1-13]

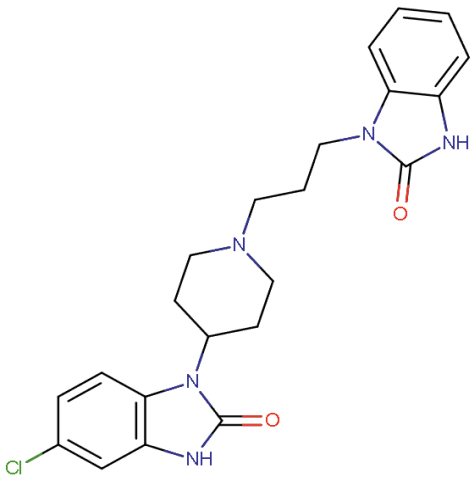


Figure 1: Chemical Structure of Domperidone.

1.2 DRUG PROFILE OF CINNARIZINE

Cinnarizine, initially produced by Janssen Pharmaceuticals in 1955, is an antihistamine medication used to treat vestibular problems and motion sickness. It works as a calcium channel blocker, specifically targeting the central vestibular system and disrupting signal

transmission between the inner ear's vestibular apparatus and the vomiting center of the hypothalamus. Cinnarizine can also be considered a nootropic due to its vasorelaxation properties, resulting from calcium channel blockade, which predominantly occur in the brain. When combined with other nootropics like piracetam, cinnarizine enhances the effect of increasing brain oxygen supply. The IUPAC designation for Cinnarizine is 1-(diphenylmethyl)-4-[(2E)-3-phenylprop-2-en-1-yl] piperazine. It has a molecular weight of 368.514 g/mol and the chemical formula $C_{26}H_{28}N_2$. Cinnarizine inhibits the contraction of vascular smooth muscle cells by inhibiting L-type and T-type voltage-gated calcium channels. It can also bind with dopamine D2 receptors, histamine H1 receptors, and muscarinic acetylcholine receptors.[14-24]

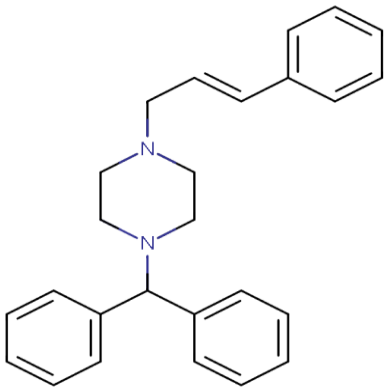


Figure 2: Chemical Structure of Cinnarizine.

After a thorough literature study,[25-33] the authors analyzed that there have been relatively a few spectroscopic and liquid chromatographic techniques published for simultaneously estimating Domperidone and Cinnarizine. As a result, there is a need to create a simple, new, speedy, exact, sensitive, and selective RP-HPLC technique for estimating Domperidone and Cinnarizine in its tablet dosage form.

2. MATERIALS AND METHODS

2.1 APPARATUS & CHEIMCALS

Table 1: List of apparatus.

S.no	Name	Model	Manufacturer
1	HPLC	Waters 2690	ALLIANCE
2	pH meter	Model 152	RI
3	Weighing Balance	SAB 203 L	Scale tech
4	Pipettes, Beakers and Burettes	NA	Borosil Class-A
5	Ultra Sonicator	PSA-10A	DIGITAL PRO

Table 2: List of chemicals.

S. No	Name	Grade	Batch No
1	Water (Milli Q / HPLC Grade water)	HPLC	P24E100596
2	Acetonitrile	HPLC	R022F24
3	Orthophosphoric acid	AR, ACS	A015B24

2.2 PREPARATION OF SOLUTIONS

BUFFER PREPARATION

1.5ml of Orthophosphoric acid was transferred into a 1500 ml of HPLC grade water and filtered with 0.45µm filter paper and sonicated for ten min.

MOBILE PHASE PREPARATION

1400 ml of buffer solution and 600 ml of acetonitrile (70:30) was mixed well in a volumetric flask and sonicated for 10 minutes.

DILUENT PREPARATION

Mobile phase was used as a diluent throughout the study.

STANDARD PREPARATION

31.50 mg of Domperidone and 42.25 mg of Cinnarizine were precisely weighed and put to two separate 100 mL volumetric flasks. 60 mL of diluent was then added and sonicated for up to 5 minutes. The volume was brought up to the mark with diluent. Then 4ml of each solution was put into a 50ml volumetric flask, and the volume was adjusted to the mark using the same diluent.

SAMPLE PREPARATION

Equivalent powder from 20 tablets was accurately taken from VOXZI tablets containing Domperidone 15mg and Cinnarizine 20mg was transferred to a 100 mL volumetric flask. 60 mL of diluent was put in and sonicated for up to 5 minutes. The volume has been brought up to the mark with diluent. Then, 4ml of the aforesaid solution was then transferred to a 50ml volumetric flask, and the final volume was adjusted to the mark using the same diluent.

OPTIMIZED CHROMATOGRAPHIC CONDITIONS

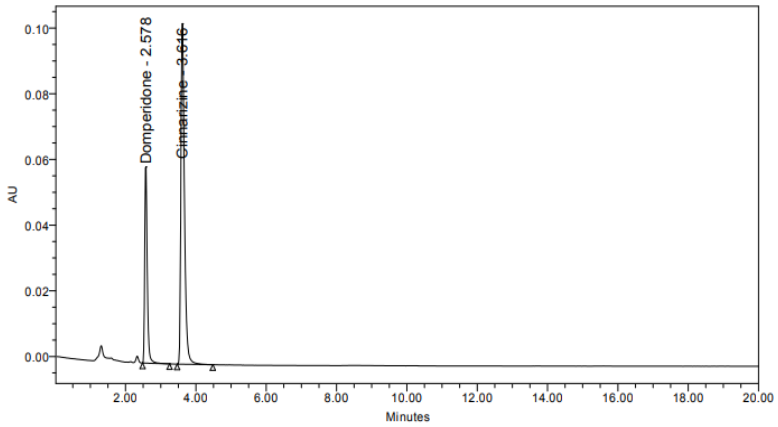
After performing various trials in isocratic mode, the optimized chromatogram was obtained at 226nm with a flow rate of 1.2ml/min using Phosphoric acid buffer: Acetonitrile (70:30). The Sample temperature was maintained at $20^{o}\pm 5^{o}C$. Peaks were well resolved using a Welchrom column of 250mm x 4.6mm, 5µm particle size at an ambient column temperature

for 20 min run time.

3. RESULTS And DISCUSSION

3.1 System Suitability

In chromatography, system suitability refers to a set of tests performed to confirm that the chromatographic system (including equipment, electronics, analytical processes, and samples) is operational prior to beginning an analysis. These tests are necessary to establish that the system's performance is appropriate for the intended application and to assure the dependability of analytical results in compliance with the ICH requirements.[34]



	Peak Name	RT	Area	% Area	Height	USP Plate Count	USP Tailing	USP Resolution	K Prime
1	Domperidone	2.578	303932	29.88	59652	5891	1.3		2
2	Cinnarizine	3.616	713350	70.12	103299	6409	1.5	7	3

Figure 3: System suitability for standard chromatogram.

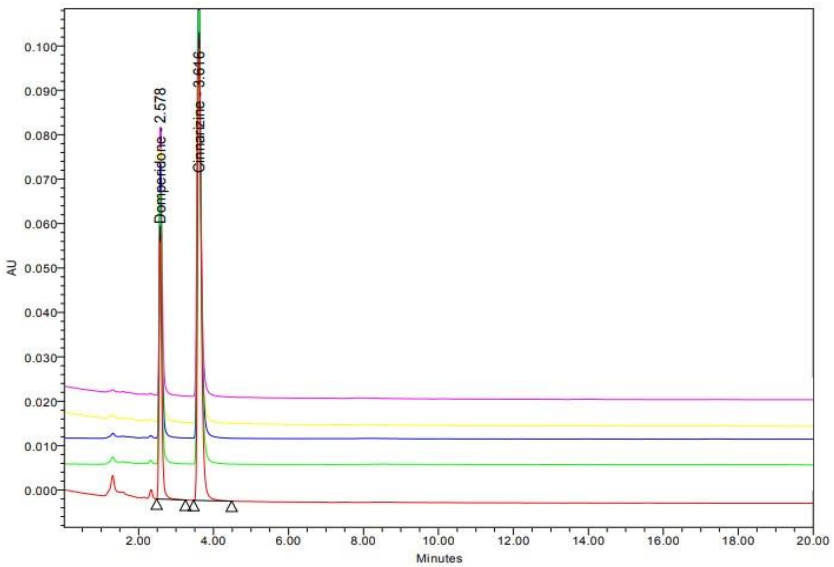


Figure 4: Overlay of System suitability for standard chromatograms.

Table 3: System suitability results.

		Domperidone		Cinnarizine	
		Retention Time	**Area**	**Retention Time**	**Area**
1	Mean*	2.585	303985.8	3.608	712671.8
2	Std. Dev	0.004	788.5	0.006	1795.2
3	% RSD	0.17	0.3	0.16	0.3

***** Average of five replicate injections

Discussion: This method successfully passed the system suitability criteria, as shown by a tailing factor NMT 2.0, theoretical plate value exceeding 2000, and the %RSD value below 2.0%.

3.2 SPECIFICITY

In chromatography, specificity refers to a method's capacity to quantify the analyte in the presence of matrix components, degradation products and contaminants or other analytes. A high level of specificity indicates that the chromatographic technique can accurately extract and identify the target compound while avoiding interference from other substances in the sample.

Blank

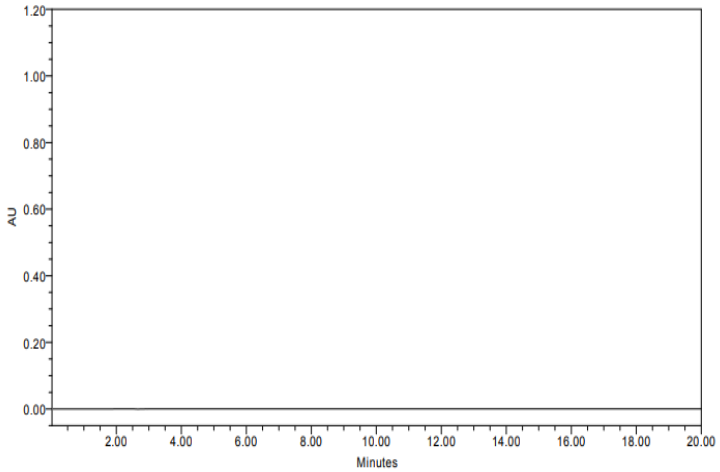


Figure 5: Blank chromatogram.

Discussion: The specificity chromatogram for the blank showed no interference with the primary peak, indicating that the technique is specific.

3.3 ACCURACY

The correctness of an analytical procedure refers to how closely the test findings match the real value. To test accuracy, sample solutions with concentrations of 50%, 100%, and 150%

of the target analyte are injected into the system, and the percentage recovery is computed using the predicted values.

Table 4: Results for Accuracy.

S.No	Sample solution concentration*	Domperidone		Cinnarizine	
		% RSD	Recovery %	% RSD	Recovery %
1	50%	0.51	99.76%	0.35	99.85%
2	100%	0.45		0.79	
3	150%	0.26		0.55	

***** Average of three replicate injections

Discussion: The RSD percentage does not exceed 2.0%. The approach is considered accurate because the percentage recovery acceptability criterion for Domperidone and Cinnarizine ranges between 98.0% and 102.0%.

3.4 PRECISION

Consistency and reproducibility relates to getting the same findings while examining the same sample several times under the same conditions. Precision quantifies the variability or dispersion in these data and is commonly stated in statistical terms like Standard deviation (SD), Relative standard deviation (RSD) and Coefficient of variation (CV).

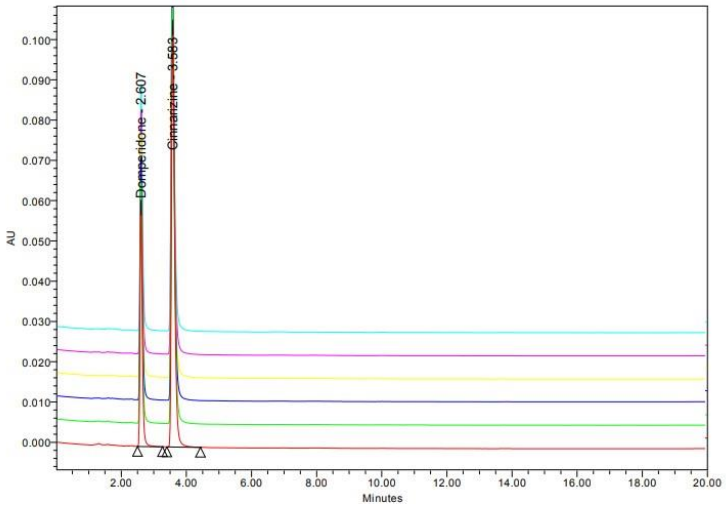


Figure 6: Overlay precision chromatograms of Domperidone and Cinnarizine

Table 5: Method precision results for Domperidone and Cinnarizine.

S. No	Peak Name*	Average	SD	% RSD
1	Domperidone	304457	0.52	0.5
2	Cinnarizine	710745	0.19	0.2

***** Average of six replicate injections

Discussion: The RSD percentage does not exceed 2.0%. The approach is regarded as precise since the precision values are within the acceptable range for Domperidone and Cinnarizine.

3.5 LINEARITY

Linearity in chromatography refers to the relation between analyte concentration and response of the detector. It defines how well the detector response matches fluctuations in analyte concentration across a certain range. A linear chromatogram indicates that the detector response (peak area or height) changes in proportion to the analyte concentration. This feature is necessary for the precise and accurate measurement of compounds in samples using chromatographic techniques. Domperidone and Cinnarizine were made in five concentrations, and each concentration was injected three times to test linearity. Linearity graph was drawn by plotting analyte concentration on x-axis and peak area on y-axis.

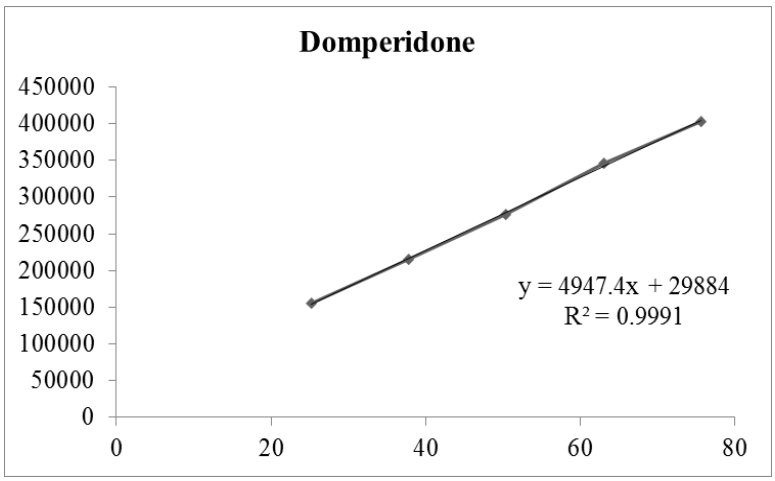


Figure 7: Linearity graph for Domperidone.

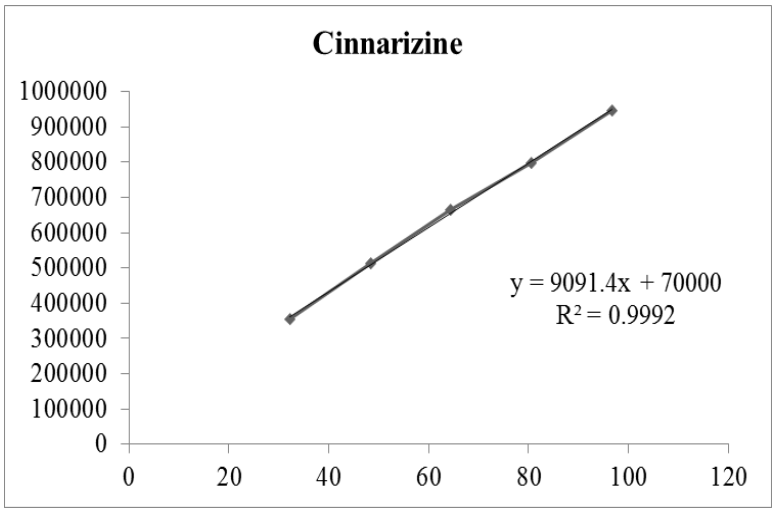


Figure 8: Linearity graph for Cinnarizine.

Table 6: Results for linearity.

DOMPERIDONE		CINNARIZINE	
Conc. in PPM*	**Peak Area**	**Conc. in PPM***	**Peak Area**
25.2	156208	32.2	356062
37.8	215487	48.3	512454
50.4	275898	64.4	665487
63	345878	80.5	798548
75.6	402701	96.6	944871
Regression Equation	y = 4947.4x + 29884	Regression Equation	y = 9091.4x + 70000
Linearity Correlation Coefficient (R^2)	0.9991	Linearity Correlation Coefficient (R^2)	0.9992

***** Average of three replicate injections

Discussion: The R^2 values are NLT 0.99 for Domperidone and Cinnarizine, indicating that the method is linear.

3.6 RANGE

The range is the period between the biggest and lowest analyte concentrations in the sample throughout which the technique has been shown to be precise, accurate, and linear.

Table 7: Range Values for Domperidone & Cinnarizine.

Percentage of solution	% RSD for Domperidone	% RSD for Cinnarizine
50%	0.27%	0.37%
100%	0.27%	0.34%
150%	0.23%	0.25%

BRACKETING STANDARD

Bracketing is an analytical approach in which samples are evaluated at the maximum and minimal limits of a specific range to ensure accuracy and precision over the whole range.

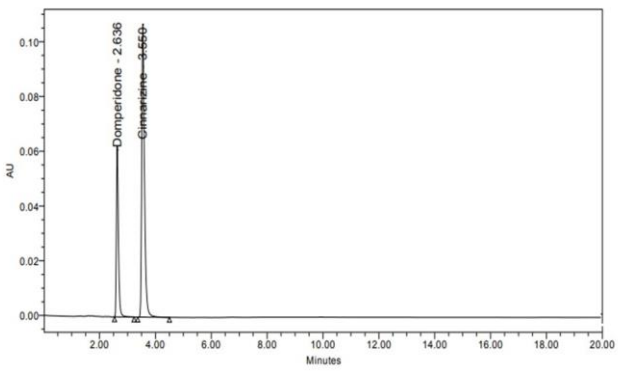


Figure 9: Sample solution Bracketing Standard chromatograms

METHOD APPLICATION TO THE ANALYSIS OF DOMPERIDONE AND CINNARIZINE

The proposed method was used to determine simultaneously Domperidone and Cinnarizine in commercially available tablet dosage form. The assay findings are reported in the table below. It was discovered that no dosage form excipients interfered with their analysis, indicating that the approach is suitable for routine quality control work.

Table 8: %Assay of Domperidone and Cinnarizine.

VOXZI Tablets		
	Labeled claim (mg)	**%Assay***
Domperidone	15	99.48%
Cinnarizine	20	98.79%

***** Average of six replicate injections

SUMMARY AND CONCLUSION

The study successfully established and validated a particular, new, and accurate RP-HPLC technique for simultaneously estimating Domperidone and Cinnarizine in Tablet Dosage Forms.

Parameters	**Domperidone**	**Cinnarizine**
% Recovery in Accuracy	99.76%	99.85%
% RSD in Precision	0.50%	0.20%
Linearity Correlation coefficient	0.9991	0.9992
% Assay	99.48%	98.79%

The developed and validated method have been carefully executed, yielding a reliable and efficient analytical approach. This method is designed to ensure that these two drugs, often used together in treatments, can be accurately measured in combined dosage forms.

The specificity of the method was thoroughly tested, and it was found to precisely identify Domperidone and Cinnarizine without interference from other substances that might be present in the sample. This is crucial because it means that the method can reliably differentiate these drugs from other components, such as impurities or degradation products, which is vital for ensuring the safety and efficacy of the Tablet Dosage Form.

In terms of linearity, the method proved to be highly dependable. With a correlation coefficient of 0.99 for both drugs, the results show a strong and consistent relationship between the concentration of the drugs and the response from the detector. This linearity

across a range of concentrations means that the method can be used confidently to measure different doses of these drugs, from low to high concentrations, without losing accuracy.

Accuracy is another key aspect that was rigorously validated. Through recovery studies, where known amounts of the drugs were added to samples and then measured, the method consistently produced results within the desired range of 98% to 102%. This high level of accuracy ensures that the method can reliably measure the actual amount of drug in a sample, which is essential for maintaining the quality and therapeutic effectiveness of the medication.

Precision, a measure of the method's consistency, was demonstrated through repeated tests. The method showed very low variability, with a relative standard deviation (RSD) of less than 2.0%. This indicates that the method produces stable and reproducible results, which is critical for routine quality control in a pharmaceutical setting.

The method also performed well in terms of column efficiency, capacity factor, and tailing factor, which are technical parameters that influence the quality of the separation process in chromatography. Meeting the required standards for these parameters ensures that the method is not only accurate and precise but also efficient and reliable over time.

ACKNOWLEDGMENT

All authors are thankful to Principal and management of College of Pharmacy, Srinivasararao College of Pharmacy for provides facilities for this work.

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