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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF PERINDOPRIL AND INDAPAMIDE USING RP-HPLC

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Keywords:

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ABSTRACT: A rapid and robust RP-HPLC method was developed and validated for the simultaneous quantification of Perindopril and Indapamide. Chromatographic separation was achieved on a Zodiac C18 column (4.6 × 150 mm, 5 µm) at 38°C using a mobile phase of acetonitrile and water (40:60 v/v) with a flow rate of 1.0 mL/min. Detection was performed at 223 nm, and the injection volume was 10 µL, with a total run time of 10 minutes. The method was validated for accuracy, precision, linearity, and reproducibility. Calibration curves demonstrated excellent linearity with correlation coefficients of 0.9991 for Perindopril and 0.9998 for Indapamide. Accuracy and precision studies showed % purity values of 99.86% for both drugs, confirming the reliability of the method. The developed RP-HPLC method is rapid, precise, and suitable for routine simultaneous estimation of Perindopril and Indapamide in pharmaceutical formulations.

INTRODUCTION: Perindopril is a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor and a pro-drug of Perindoprilat **Fig. 1** [1]. Chemically, it is (2S, 3aS, 6aS)-1-[(S)-N-(1-ethoxycarbonyl - 3 - phenylpropyl) - L - alanyl] octahydro-1H-quinazoline-2,4-dione [2]. It is widely used in the management of hypertension and cardiovascular disorders [3]. Indapamide **Fig. 2** [4] is a non-thiazide indole derivative of chloro-sulphonamide used as an oral antihypertensive and diuretic agent. Chemically, it is 4-chloro-N-(2-methyl-2, 3-dihydro-1H-indol - 1-yl)-3 - sulfamoyl benzamide [5]. Several spectrophotometric and chromatographic methods have been reported for the estimation of these drugs individually and in combination in bulk and pharmaceutical dosage forms [6–12].

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However, there remains a need for a simple, precise, and reliable analytical method for their simultaneous determination. Therefore, a novel RP-HPLC method was developed and validated for the accurate quantification of Perindopril and Indapamide in bulk and formulations in accordance with ICH Q2 (R1) guidelines [13–20].

Perindopril:

IUPAC Name: (2S, 3aS, 7aS)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxopentan-2-yl] amino} propanoyl]-octahydro-1H-indole-2-carboxylic acid).

pKa value: 3.79&5.48

Drug Category: Angiotensin-converting enzyme (ACE) inhibitor. The chemical structure of Perindopril is shown in **Fig. 1.**

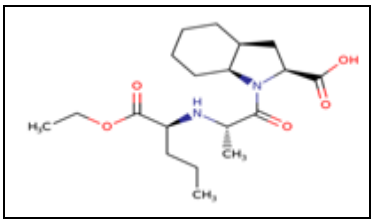

FIG. 1: CHEMICAL STRUCTURE OF PERINDOPRIL

Indapamide:
IUPAC Name: 4-chloro-N-(2-methyl-2, 3-dihydroindol-1-yl)-3-sulfamoylbenzamide

pKa value: 8.8 ± 0.2.

Drug Category: Thiazide-like diuretic. The chemical structure of Indapamide is shown in **Fig. 2.**

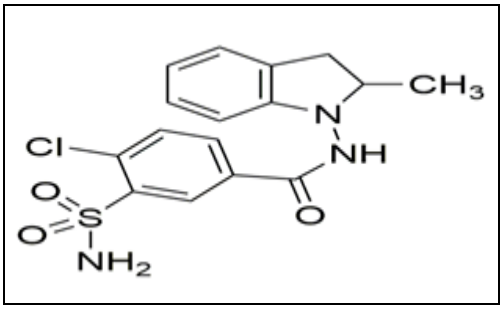

FIG. 2: CHEMICAL STRUCTURE OF INDAPAMIDE

MATERIALS AND METHODS:

Preparation of Mobile Phase: Accurately measured 400 mL (40%) of acetonitrile and 600 mL (60%) of water were mixed, degassed in an ultrasonicator for 15 minutes, and filtered through a 0.45 µm membrane filter under vacuum.

Diluent Preparation: The mobile phase itself was used as the diluent.

Preparation of Standard Solution: Accurately weigh and transfer 10 mg each of Perindopril and Indapamide into a 10 mL volumetric flask, dissolve in 7 mL diluent, sonicate, and make up the volume to mark. From this stock, pipette 1.0 mL of Perindopril and 0.5 mL of Indapamide into another 10 mL volumetric flask and dilute to volume with diluent.

Preparation of Sample Solution: Crush tablets and weigh an amount equivalent to 10 mg each of Perindopril and Indapamide, dissolve in 7 mL of diluent, sonicate, and dilute to volume. Pipette 1.0 mL of this solution into a 10 mL volumetric flask and dilute to the mark.

Procedure: Inject three replicate injections of standard and sample solutions.

Calculate assay using the formula:

%Assay = (Sample Area) / (Standard Area) × (Weight of Standard) / (Dilution of standard) × (Dilution of Sample) / (Weight of Sample) × (Weight of Tablet) / (Label Claim) × Purity / 100 × 100

The percentage purity of Perindopril and Indapamide in the formulation was 100.14% and 99.5%, respectively **Table 1.**

TABLE 1: ASSAY RESULTS OF PERINDOPRIL AND INDAPAMIDE TABLETS

S. no.	Name of Compound	Label Claim	Amount Taken	% Purity
1	Perindopril	15mg	12.8	100.14%
2	Indapamide	25mg	23.6	99.5%

Chromatographic Conditions:
Column: Zodiac C18 (150 × 4.6 mm, 5µm)

Mobile Phase: Acetonitrile: Water (40:60 % v/v)

Flow rate: 1.0 mL/min

Detection Wavelength: 233 nm

Injection Volume: 10 µL

Column Temperature: Ambient

Runtime: 10 min

Retention Times: Perindopril 2.343 min, Indapamide 3.281 min.

Representative chromatograms of the standard mixture are shown in **Fig. 3**, indicating clear separation of both analytes.

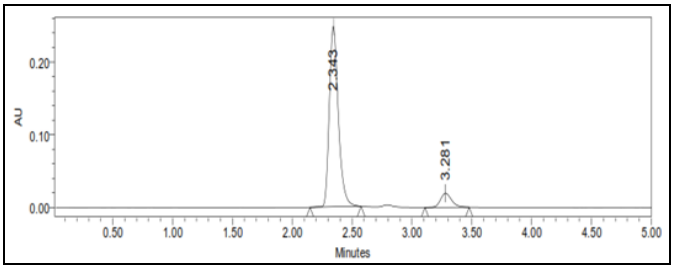

FIG. 3: REPRESENTATIVE CHROMATOGRAM OF PERINDOPRIL AND INDAPAMIDE

RESULTS AND DISCUSSION:

Precision: The precision of the developed RP-HPLC method was evaluated by performing intra-day and inter-day studies. The %RSD values for intra-day precision were 0.17% for Perindopril and 0.42% for Indapamide, while inter-day precision showed values within 2% for both drugs **Table 2**. These low %RSD values indicate excellent

repeatability and reliability of the method. This confirms that the method provides consistent and reproducible measurements suitable for routine analysis.

TABLES 2: INTRA-DAY AND INTER-DAY PRECISION RESULTS

	Intra-day precision (peak area)		Inter-day precision (peak area)	
Injections	**Perindopril**	**Indapamide**	**Perindopril**	**Indapamide**
1	1265784	65874	1358754	66985
2	1269853	65879	1365825	66258
3	1265875	65982	1374582	66479
4	1265846	65289	1385754	66358
5	1269852	65878	1369856	66259
Mean	1267442	65780.4	1368885.6	66554.17
Std. Dev.	2200.721	278.4444	10362.82	343.8217
%RSD	0.17	0.42	0.76	0.52

Accuracy: Accuracy was assessed through recovery studies at 50%, 100%, and 150% levels. The % recovery ranged between 99.83% and 100.34% for both Perindopril and Indapamide **Table 3**, indicating that the method is highly accurate and free from interference. These results are consistent with literature reports where recoveries for these drugs in combination formulations ranged from 98% to 101%, confirming the reliability of the method for quantitative determination in pharmaceutical dosage forms.

TABLE 3: RECOVERY STUDY RESULTS FOR PERINDOPRIL AND INDAPAMIDE

% Level	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery
		Perindopril		
50%	641242	10	10.01	100.01%
100%	1269095	20	19.95	99.75%
150%	1907722	30	30.12	100.4%
		Indapamide		
50%	641242	10	10.02	100.02%
100%	1269095	20	19.97	99.95%
150%	1907722	30	30.10	100.33%

Linearity: The calibration curves for Perindopril and Indapamide showed excellent linearity in the concentration ranges of 10–30 µg/mL and 30–70 µg/mL, respectively. The correlation coefficients (r^2) were 0.999 for both drugs **Table 4** & **5**, **Fig. 4** & **5**, demonstrating a strong linear relationship between concentration and peak area. The slopes and intercepts indicate consistent detector response. Linearity across this range confirms that the method is suitable for detecting both low and high concentrations of these drugs in combined formulations.

TABLE 4: LINEARITY DATA FOR PERINDOPRIL

S. no.	Concentration (µg/ml)	Peak area	Perindopril	
1	10	652874	Statistical Data of the Regression Equation	
2	15	964575		
3	20	1268589	Correlation	0.999
4	25	1585745	Slope	63010
5	30	1895472	Y- intercept	11037

TABLE 5: LINEARITY DATA FOR INDAPAMIDE

S. no.	Concentration (µg/ml)	Peak area	Indapamide	
1	30	44482	Statistical Data of the Regression Equation	
2	40	58856		
3	50	72584	Correlation	0.999
4	60	85789	Slope	1421
5	70	99583	Y- intercept	997.6

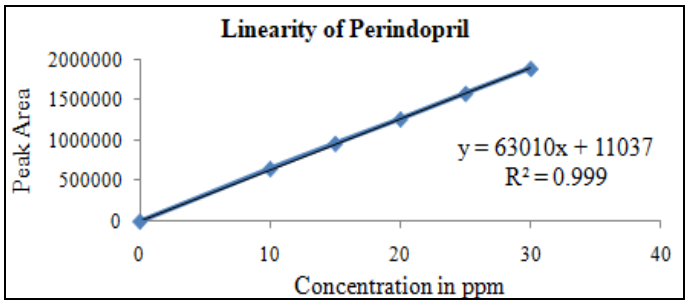

FIG. 4: LINEARITY GRAPH OF PERINDOPRIL

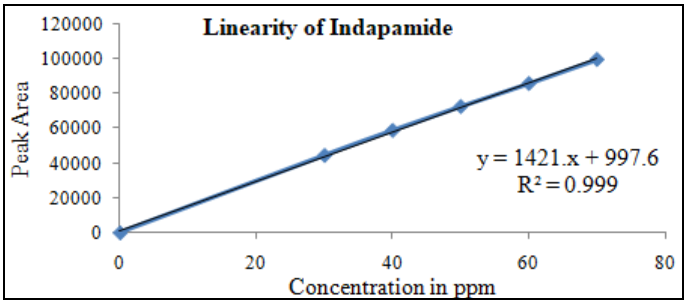

FIG. 5: LINEARITY GRAPH OF INDAPAMIDE

Limit of Detection (LOD) and Limit of Quantization (LOQ): The LOD and LOQ were determined to be 2.68µg/mL and 8.04µg/mL for Perindopril, and 3.54µg/mL and 10.62µg/mL for Indapamide, respectively. These low values indicate the method's high sensitivity, enabling detection and quantification of even small amounts of the analytes, which is critical for quality control and stability studies

Robustness: The robustness of the developed method was evaluated by introducing small, deliberate variations in chromatographic conditions, including changes in flow rate (±0.1 mL/min) and mobile phase composition (±10%). As presented in **Table 6**, these variations did not produce any significant changes in retention time, peak area, or system suitability parameters.

The results confirm that the method remains unaffected by minor operational fluctuations, thereby demonstrating its robustness and reliability. This observation is consistent with previously reported HPLC methods for the analysis of Perindopril and Indapamide, which also exhibited stable system suitability parameters under slight method modifications.

TABLE 6: ROBUSTNESS STUDY FOR PERINDOPRIL AND INDAPAMIDE

Parameter Changed	Drug	Retention Time (min)	Peak Area	Theoretical Plates	%RSD
Flow rate +0.1 mL/min	Perindopril	2.350	1267320	4200	0.17
	Indapamide	3.290	65795	3980	0.42
Flow rate −0.1 mL/min	Perindopril	2.336	1267550	4195	0.18
	Indapamide	3.275	65810	3975	0.43
Mobile phase ±10% (ACN: Water 44:56)	Perindopril	2.348	1267450	4210	0.17
	Indapamide	3.285	65790	3990	0.41

Specificity: Specificity was confirmed by analyzing placebo solutions and standard drug solutions. No interference from excipients or degradation products was observed at the retention times of Perindopril (2.343 min) and Indapamide (3.281 min), demonstrating that the method is highly selective for both analytes in combined formulations. This ensures accurate estimation of the drugs even in the presence of common tablet excipients, consistent with literature findings.

DISCUSSION: Overall, the developed RP-HPLC method demonstrates high precision, accuracy, linearity, specificity, and robustness, making it suitable for routine quality control of combined Perindopril and Indapamide formulations. Compared to previously reported methods, this method offers a shorter runtime (10 min) and simple mobile phase composition, making it cost-effective and efficient without compromising analytical performance. The method's sensitivity, with low LOD and LOQ values, further supports its applicability for stability studies and detection of minor impurities or degradation products.

CONCLUSION: A robust, accurate, and precise RP-HPLC method has been successfully developed and validated for the simultaneous estimation of Perindopril and Indapamide in bulk and tablet formulations. The method exhibits excellent linearity, high recovery, and specificity, with assay results consistently near 100% purity. Its simplicity, reproducibility, and robustness make it highly suitable for routine quality control, stability studies, and regulatory compliance in pharmaceutical industries, providing a reliable analytical tool for combined dosage forms.

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CONFLICTS OF INTEREST: Nil

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