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RESEARCH ARTICLE

Development and Validation for Simultaneous Estimation of Perindopril and Indapamide by UPLC–UV in Tablet Dosage form

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ABSTRACT:

An ultra-performance liquid chromatography (UPLC) method with UV detection was developed for simultaneous estimation of Perindopril and Indapamide in tablet dosage form of pharmaceutical formulation. Simultaneous determination of both drugs is highly significant as this would tolerate more effective generation of clinical data and could be more cost-effective than distinct assays. The chromatography was carried out at 25 °C using an isocratic mobile phase consisting of buffer (0.1% ortho phosphoric acid in Water v/v) and acetonitrile in the ratio of 45:55% (v/v) using variable wavelength UV– Vis detector set at 254nm. Perindopril and Indapamide were eluted isocratically at a steady flow rate of 0.3mL/min, indicated reasonable good assay parameters. The retention times were around 0.8 min and 1.1 min, asymmetry factors 1.7 and 1.6, and linearity correlation coefficients were in the range 20 - 120 and 6.25 - 37µg/ml, respectively. Regression coefficient was 0.999 for both the compounds, while recovery from samples were 98.09-100.17 and 99.06–99.99% for Perindopril and Indapamide, respectively. Relative standard deviations (RSD) of intra- and inter-day precisions were < 2% for both the drugs. Specificity/selectivity experiments revealed the absence of interference from excipients. From the above parameters indicated that the present developed method is precise, accurate, reproducible and specific for desired drug analysis. Moreover, it can also be used for routine simultaneous estimation of Perindopril and Indapamide in combinations tablets of pharmaceutical drug products.

KEYWORDS: Perindopril, Indapamide, Ultra performance liquid chromatography, Pharmaceuticals, Drug separation, Analytical methods.

INTRODUCTION:

Perindopril and Indapamide are very important drugs for treatment of high blood pressure in recent days[1-4]. These two drugs are also used to prevent heart attacks in patients with a certain type of heart disease (stable coronary artery disease). Moreover, they can be used individually or combination with other drugs to reduce the risk of heart attack or death caused by heart problems in patients[5-9].

Perindopril is chemically (2*S*, 3aS, 7aS)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxopentan-2-yl] amino} propanoyl]-octahydro-1*H*-indole-2-carboxylic acid (fig. 1a) an angiotensin-converting enzyme (ACE) inhibitor, which works by relaxing blood vessels and helps to lower blood pressure. Whereas, Indapamide is chemically 4-

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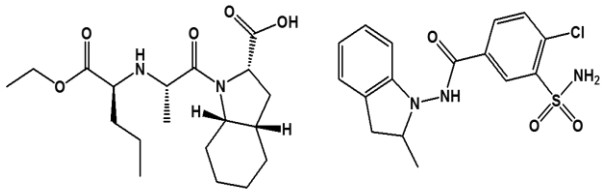
chloro-*N*-(2-methyl-2,3-dihydro-1*H*-indol-1-yl)-3-sulfamoylbenzamide (fig. 1b) a thiazide diuretic (water pill) that helps prevent patients body from absorbing too much salt, which can cause fluid retention (edema) in people with congestive heart failure[10].

Perindopril and Indapamide drugs are available at present in combination therapy treatment method[11]. The motivation behind use of this drug mixture is that while treatment of hypertension in patients, blood pressure (BP) is not effectively controlled by monotherapy method[12]. Combination treatment with Perindopril and indapamide successfully decreases the BP in patients with essential hypertension[13-14]. Furthermore, simultaneous determination of both drugs is highly significant, which would tolerate more effective generation of clinical data and could be more cost-effective than distinct assays.

Simultaneous estimation of Perindopril and Indapamide have been studied[15-30] various spectrophotometric UV-Vis, RP-HPLC, and HPLC methods for estimation of individually or in combination with other drugs. To the best of our knowledge, simultaneous estimation of Perindopril and Indapamide in pharmaceutical formulations by an ultra-performance liquid chromatography (UPLC) method with UV detection (UPLC–UV) was not reported so for. In fact, UPLC is a modern technique which gives a new direction for liquid chromatography, which enhances essentially in three areas: "speed, resolution and sensitivity" compared to other available analytical methods. In this context, we are interested in developing simple, specific, accurate and precise UPLC using direct UV-detection method for the simultaneous estimation of Perindopril and Indapamide in commercially available tablet dosage form and also in-house prepared pharmaceutical formulations. Additionally, the proposed method can be used in industries that deal with estimation of Perindopril and Indapamide in tablet dosage form[31-48].



(a) Perindopril (b) Indapamide

EXPERIMENTAL SECTION:

Instrumentation:

Integrated Ultra performance liquid chromatographic systems Acquity from Waters Corporation (Chromatographic and Spectrophotometric Division, USA) consisted of a binary gradient system, a high speed auto-sampler, a column oven and a UV– Vis detector. Acquity UPLC, HSS C18 100x2.1mm, 1.8µm analytical column from USA, was used as stationary phase. Chromatograms were recorded and integrated on PC installed with Empower software.

Reference substances, reagents and chemicals:

Ortho phosphoric acid was procured from Merck and distilled water was obtained from a Milli-Q system Millipore, USA. Acetonitrile purchased from Sigma Aldrich, USA. All the chemicals and reagents were of analytical or reagent grade used as purchased without any further purification.

Chromatographic conditions:

Isocratic mobile phase consisted of a buffer (0.1% ortho phosphoric acid in water v/v): Acetonitrile in 45:55% v/v. The mobile phase was filtered and degassed through membrane filter of 0.45µm porosity under vacuum. A constant flow rate of 0.3mL/min was employed throughout the analysis. Variable UV-Vis detector was used with wavelength was set at 254 nm. All pertinent analyses were performed at 25°C, in which 0.20µL volume of the solution was injected into the column with injection run time of 2 min. Water/Acetonitrile in the ratio of 1:1 was used as diluent.

Samples:

Test samples were of tablet dosage formulations and purchased from the Serdia Pharmaceuticals India Pvt Ltd with composition of 8mg Perindopril, 2.5mg Indapamide (Brand Name: Coversyl Plus HD).

Solution preparation:

Perindopril and Indapamide standard solution:

Standard solutions were prepared by transferring accurately about 8mg of Perindopril and 2.5mg of Indapamide working Standards into a two separate 10 mL volumetric flasks. A 3/4th volume of diluent was added in to two volumetric flasks followed by sonicated for 5 min of each. Later, these solutions were diluted to 10mL volume with the diluent and mixed well. From above two stock solutions, 1 mL from each was transferred into 10mL volumetric flask and made up to the volume with diluent.

Estimation from formulations:

Exactly 20 tablets were weighed and converted to powder form; weight equivalent to one tablet was transferred into a 10mL volumetric flask. To this solution, 5mL of diluent was added and sonicated for 25 min followed by further diluent was added to the volume of 10mL. Later this sample solution was filtered and from this filtrate solution, 1mL was pipetted out into a 10mL volumetric flask and made up to 10mL with diluent.

Quantitation:
Peak areas were recorded for Perindopril and Indapamide drugs, which were taken into account for quantifying the label amount in percentages.

RESULTS AND DISCUSSION:

Chromatography:
To develop a suitable and robust LC method for the determination of Perindopril and Indapamide by UV detection, several trails with different mobile phases and columns were employed to achieve the best signal response and retention time[15,44]. From the above attempts, the mobile phase consisting of buffer with 0.1 % ortho phosphoric acid in water (v/v)/ acetonitrile in 45:55% ratio (v/v). The mobile phase was filtered and degassed through membrane filter of 0.45µm porosity under vacuum. A constant flow rate of 0.3mL/min was employed throughout the analysis. Variable UV-Vis detector with wavelength set at 254nm was used. All the pertinent analyses were performed at 25°C. The solution of 0.20µL volume was injected into the column with injection run time was around 2 min. The above mentioned optimized chromatographic conditions were found to be appropriate, allowing good signal response as shown in figure 2.

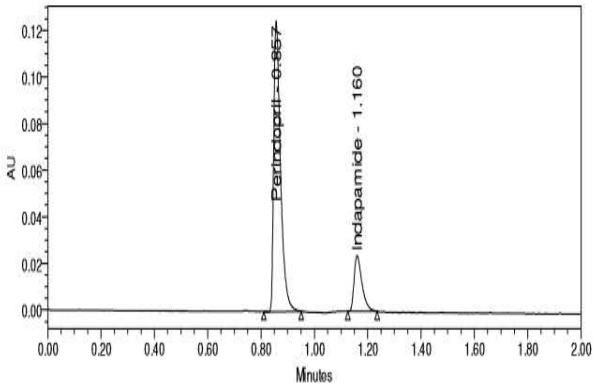


Fig. 2: Plot shows the results of retention times of Perindopril and Indapamide compounds with Mobile phase: Buffer (0.1 % ortho phosphoric acid in water v/v): Acetonitrile in 45:55 % (v/v) ratio.

Optimization of method by UPLC-UV:
Composition of the mobile phase can affect the analyte's retention time as well as the detection sensitivity[15,27]. To optimize our results, two other attempts with different mobile phase compositions with retention times and detection sensitivity are shown in fig 3, were carried out. From these attempts we optimized that when mobile buffer (0.1 % ortho phosphoric acid in water v/v): Acetonitrile in 45:55 % (v/v) ratio shows good retention time, 0.857 and 1.160 min with reasonably good detection sensitivity (Fig 2).

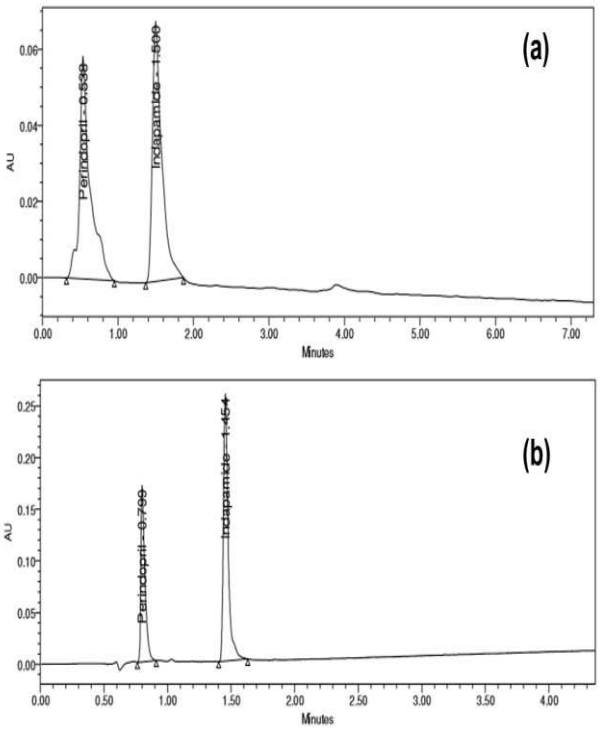


Fig. 3: Plot shows the results of retention times of Perindopril and Indapamide compounds (a) Mobile phase: Buffer (0.1 % ortho phosphoric acid in water v/v): Acetonitrile in 70:30 % v/v, (b) Mobile phase: Buffer (0.1 % ortho phosphoric acid in water v/v): Acetonitrile in 50:50 % v/v

Method validation:
Test method for the determination of Perindopril and Indapamide was validated to include the essential demands of International Council for Harmonization (ICH) guidelines[15,44]. Parameters like specificity, linearity, accuracy, precision, range, robustness, solution stability and system suitability were examined.

Specificity:
No interferences were observed due to obvious presence of excipients.

Linearity:
Peak areas versus concentration in ppm were plotted for Perindopril and Indapamide at the concentration range between 25.0 and 150.0% of target level. Perindopril showed linearity in the range of 20–120 ppm, and Indapamide showed linearity in the range of 6.25–37 ppm respectively. Linear regression equations and correlation coefficient (r^2) for Perindopril and Indapamide are provided below:

$Y_{Perindopril}$ 2660.1x + 3197.4 (r^2 0.9995).
$Y_{Indapamide}$ 1948.8x + 534.14 (r^2 0.9986).

Accuracy:
Accuracy of the proposed UPLC determination was evaluated from the assay results of the components. Accuracy was done by performing the assay of samples and calculated the peak area responses of different samples by recovery method. Appropriate portions of stock solution were produced in the concentrations of 50.0 to 150.0 % of target level. Recovery of samples for Perindopril and Indapamide is shown in Table 1 and 2, respectively.

Precision:
Instrumental precision was determined by six replicate determinations of standard solution and relative standard deviation was calculated for peak areas were found to be % for Perindopril and Indapamide.

Method precision or intra-assay precision was performed by preparing six different samples from the same sample pool. Each solution was injected once under the same conditions and mean value of peak area response for each solution was taken. The relative standard deviation of Perindopril and Indapamide in six sample solutions was calculated. Relative standard deviations obtained for Perindopril was 0.58 % and for Indapamide was 0.45% respectively.

Table1: Accuracy data: analyte recovery (Perindopril)

Level	Theoretical amount (ppm)	Theoretical (% of target level)	Determined Amount (ppm)	Recovery (%)
1	40	50.00	39.23459	98.09
	40	50.00	39.57218	98.93
	40	50.00	39.49361	98.73
2	80	100.00	78.89135	98.61
	80	100.00	78.68797	98.36
	80	100.00	79.44023	99.30
3	120	150.00	118.6162	98.85
	120	150.00	120.2075	100.17
	120	150.00	118.0711	98.39

Table 2. Accuracy data: analyte recovery (Indapamide)

Level	Theoretical amount (ppm)	Theoretical (% of target level)	Determined Amount (ppm)	Recovery (%)
1	12.5	50.00	12.45375	99.63
	12.5	50.00	12.46658	99.73
	12.5	50.00	12.41884	99.35
2	25	100.00	24.78742	99.15
	25	100.00	24.76432	99.06
	25	100.00	24.99841	99.99
3	37	150.00	36.41576	98.42
	37	150.00	36.95426	99.88
	37	150.00	36.67243	99.11

Range:
Range of a method is defined as the lower and higher concentrations for which the method has adequate accuracy, precision and linearity. To demonstrate the range, three samples each of lower concentration (50% of target level), sample concentration (100% of target level) and higher concentration (150% of target level) were prepared similar to accuracy samples by spiking the drug substance into blank matrix (placebo). Each sample was injected in triplicate at lower concentrations, mean recovery of Perindopril and Indapamide were found to be 98.58% and 99.57% respectively. Relative standard deviation obtained from these determinations was found to be 0.45% and 0.20% for Perindopril and Indapamide, respectively. At 100% level concentration, mean recovery of Perindopril and Indapamide were found to be 98.76% and 99.40% respectively. Relative standard deviation obtained from these determinations was found to be 0.49% and 0.52% for Perindopril and Indapamide, respectively. At higher concentration, mean recovery of Perindopril and Indapamide were found to be 99.14% and 99.14%, respectively. Relative standard deviation obtained from these determinations was found to be 0.93 % and 0.73% for Perindopril and Indapamide, respectively.

Robustness:
Robustness of the proposed method was performed by keeping chromatographic conditions constant with following deliberate variations.

i. Changing the column temperature from 23°C to 27 °C.
ii. Changing the organic content (Acetonitrile) in mobile phase composition from 50% to 60 %.
iii. Changing the flow rate from 0.27 to 0.33mL/min.

Standard solution was injected for six times in replicate for each minor change. System suitability parameters like peak asymmetry, theoretical plates, USP resolution between Perindopril and Indapamide and relative standard deviation of peak areas were recorded for Perindopril and Indapamide peaks and found to be within acceptable limits. Moreover, it was observed that

during the experiments, slight change in column temperature by varying organic content in mobile phase composition and also flow rate does not disturb the method, indicated by similar yields and system suitability.

System suitability:

System suitability tests were performed on chromatograms obtained from the standard solutions to the check parameters such as peak retention, theoretical plate count, peak asymmetry and resolution etc. Results obtained from six replicate injections of standard solution performed by the proposed method are summarized in Table 3.

Table 3: System suitability parameters of the proposed method.

(System suitability results from the standard solution injected in six replicates with proposed method chromatographic conditions.)

Perindopril peak results				**Indapamide peak results**				
Standard Solution	**Retention time (min)**	**Peak asymmetry**	**Theoretical plates**	**Standard Solution**	**Retention time (min)**	**Peak asymmetry**	**Theoretical plates**	**Resolution between Per & Ind**
Inj-1	0.856	1.77	5957	Inj-1	1.160	1.58	8254	6.2
Inj-2	0.857	1.76	5462	Inj-2	1.160	1.60	6910	5.8
Inj-3	0.857	1.75	5730	Inj-3	1.160	1.64	7474	6.0
Inj-4	0.857	1.73	5498	Inj-4	1.160	1.59	7677	5.9
Inj-5	0.857	1.77	6441	Inj-5	1.160	1.68	6855	5.8
Inj-6	0.857	1.73	5966	Inj-6	1.161	1.60	6969	5.8

Solution stability:

In order to check the solution stability standard solution was kept for 24 hours and similar chromatograms experiments were performed. The chromatographic parameters observed were acceptable limits for system suitability parameters. Also the percentage of relative standard deviation for the peak areas of Perindopril and Indapamide was found to be < 2%.

CONCLUSION:

An ultra-performance liquid chromatography method based on UV detection has been developed and validated for determination of Perindopril and Indapamide in pharmaceutical formulations (solid dosage form). This method is specific, simple, rapid, accurate and precise with accurate parameters (RSD < 2.0 %) and linear r^2 < 0.99, compared with known analytical methods. The described method is suitable for routine quality control and stability studies of the drugs in pharmaceutical industry. Moreover this study also can provide a road map for developing for designing of other analytical methods for estimations of various other drugs.

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