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## ANALYTICAL METHODS OF PERINDOPRIL, REVIEW

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### ABSTRACT

Perindopril erbumine is an antihypertensive, which belongs to the category of angiotensin-converting enzyme inhibitors (ACE inhibitors) that inhibit the conversion of angiotensin I to angiotensin II. The aim of this review is to focus on a comprehensive update of analytical methods for determination of Perindopril and its metabolites in human plasma and in pharmaceutical preparations. It has been described using TLC, RP-HPLC, GC, Mass and UV methods. This review provides detailed information on separation conditions for perindopril alone, perindopril in presence of its degradation products or with its combinations.

**KEYWORDS:** Perindopril, Chromatography, HPLC, GC, MS, HPTLC, UV.

### INTRODUCTION

Perindopril, **Figure 1** is chemically: (2S,3aS,7aS)-1-[(2S)-2-[[[(2S)-1-ethoxy-1-oxopentan-2-yl]amino] propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid.

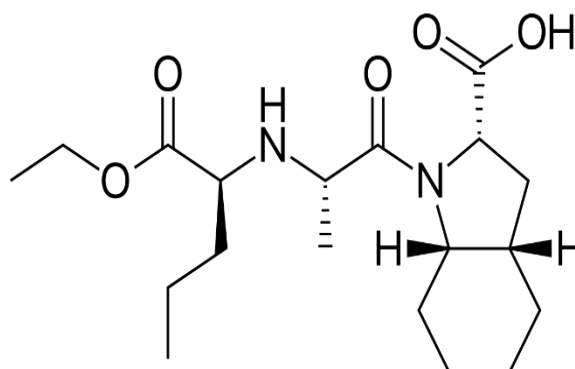
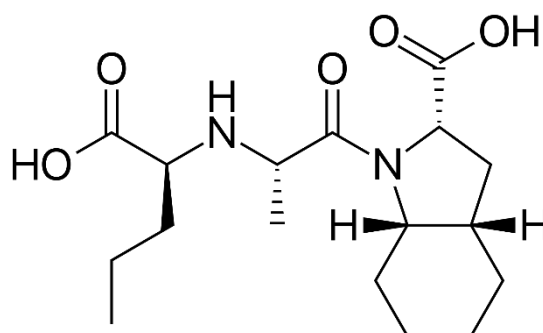


Figure 1: Perindopril

Perindopril is a pro-drug type long acting angiotensin-converting enzyme inhibitor with a perhydroindole group and no sulfhydryl radical. It is widely used in the management of essential hypertension<sup>[1]</sup> and in stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction.<sup>[2]</sup> Its main metabolic route involves hydrolytic cleavage of the ester linkage leading to its active carboxylic acid metabolite, perindoprilat, (2S,3aS,7aS)-1-[(2S)-2-[[[(2S)-1-hydroxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid,<sup>[3]</sup> **Figure 2**. Following oral administration, perindopril is rapidly absorbed, with peak plasma concentrations being reached within 1 h. Approximately 20–50% of the perindopril absorbed is converted to the active metabolite perindoprilat. Peak plasma concentrations of perindoprilat occur after 3–7 h; protein binding of perindoprilat is 10–20%. The apparent mean half-life for the majority of perindoprilat elimination is about 3–10 h, but perindoprilat has a prolonged terminal elimination half-life of 30–120 h, reflecting slow dissociation from ACE binding sites.<sup>[4]</sup>



**Figure 2: Perindoprilat**

#### DETERMINATION OF PERINDOPRIL BY RP-HPLC

Many researches for determination of Perindopril using RP-HPLC were reported and summarized in **Table 1**. A precise, an accurate, sensitive and economic HPLC method was proposed by *Suraj et al.* for simultaneous estimation of Hydrochlorothiazide and perindopril from tablet dosage forms using a mobile phase A which is a mixture of equal volumes of water (pH adjusted to 2.5 with O- phosphoric acid) and perchloric acid and mobile phase B which is 0.03% V/V solution of perchloric acid in acetonitrile at a flow rate of 1.0 ml/min with an injection volume of 20 $\mu$ l. A C<sub>8</sub> RP-Column (Zorbax XDB 150mm x 4.6 mm 5  $\mu$ m) column was used as stationary phase. Wavelength was 215nm. The retention time of Hydrochlorothiazide and perindopril were found to be 3.26 min. and 7.31 min. respectively. Linearity was obtained in the concentration range of 5-45 $\mu$ g/ml for Hydrochlorothiazide, 20-

100 µg/ml for perindopril. The method was validated statistically according to (ICH) guidelines and observed results were found in the acceptance range.<sup>[5]</sup>

Another accurate and precise RP-HPLC method was developed for the determination of perindopril in tablet dosage forms. Separation of the drug was achieved on a reverse phase C18 column using a mobile phase consisting of phosphate buffer and acetonitrile in the ratio of 65:35 v/v. The flow rate was 0.6 ml/min and the detection wavelength was 209 nm. The linearity was observed in the range of 20-100 µg/ml with a correlation coefficient of 0.9997. The proposed method was validated for its linearity, accuracy, precision and robustness. This method can be employed for routine quality control analysis of perindopril in tablet dosage forms.<sup>[6]</sup>

**Table 1: Summary of RP-HPLC methods for determination of Perindopril**

Column	Mobile Phase	Elution	Flow Rate (ml/min)	Temp. (°C)	R <sub>t</sub> (min)	LOQ µg/mL	UV λ (nm)	Ref.
Zorbax XDB C8 (250 mm × 4.6 mm I.D., 5 µm)	phosphate buffer (pH 4.5): Acetonitrile	(60:40 v/v) Isocratic	1.3	45	3.409	8	242	[7]
C18 Hypersil ODS (250 mm × 4.6 mm, 5 µm)	Methanol: Water	(70:30, v/v) Isocratic	1.0	25	NA	8.31	215	[8]
Poroshell 120 Hilic (4.6 × 150 mm, 2.7 µm)	acetonitrile–0.1 % formic acid	(20:80 v/v) Isocratic	1	25	1.95	0.4555	230	[9]
Phenomenex Luna C18 column (250 3 4.6 mm 3 5 mm)	0.2% TFAA buffer: Acetonitrile	60:40 (pH = 3 with ammonia)	1	NA	5.2	2.3	215	[10]
C18 column (250 mm × 4.6 mm, i.d., particle size 5 mm)	Methanol: Water	80:20	1	35	2.793	7.0	215	[11]
Phenomenex Luna C18 (4.6 mm × 250 mm × 10 µ)	Acetonitrile: Buffer	40:60 (v/v), pH=2.8	0.5	50	NA	NA	225	[12]
Intersil ODS C18 column (250 mm x 4.6 mm i.d., 5 µm)	Acetonitrile: Acid Phthalate Buffer (pH 3.0 ± 0.05)	(50:50, v/v) Isocratic	1	40	3.23	1.90	240	[13]
LUNA C18 (250mm x 4.6mm id)	Methanol and phosphate buffer (pH 6.8)	(85:15, v/v) Isocratic	0.8	ambient	4.62	27.06	210	[14]
Inertsil ODS3V column having 250mm x 4.6mm i.d. with 5µm	KH <sub>2</sub> PO <sub>4</sub> buffer: acetonitrile pH 3.0	(60:40 v/v) Isocratic	1.0	40°C	11.9	NA	215	[15]
NA	Acetonitrile:	(40:60, v/v)	0.8	NA	3.61	NA	217	[16]

	KH <sub>2</sub> PO <sub>4</sub> buffer (0.1% TFAA)	Isocratic						
Hypersil -BDS C18 (150 x 4.6 mm, 3μ i.d.)	NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> : Acetonitrile	(60:40, v/v) Isocratic	1.0	ambient	2.31	NA	230	[17]
HiQSiL-C-18W ODS, (250 mm × 4.5 mm i.d.), 5 μm	Acetonitrile: Water	(50:50 v/v) pH = 3.2	1.0	NA	4.5	0.041	210	[18]

### DETERMINATION OF PERINDOPRIL BY SPECTROMETER

A simple, accurate, cost effective and reproducible spectrophotometric method has been developed by *Ratnaparkhi et al.* for the estimation of perindopril erbumine in bulk and pharmaceutical dosage form. UV spectrophotometric method, which is based on measurement of absorption at maximum wavelength 213nm. The developed method was validated with respect to accuracy, linearity, precision, limit of detection, limit of quantification and Sandell's sensitivity. Beers law was obeyed in the concentration range of 4-16μg/ml having line equation  $Y=0.01350X+0.05879$  with correlation coefficient of 0.998. Results of the analysis were validated statistically.<sup>[19]</sup>

Another selective and sensitive spectrofluorimetric method was developed for the determination of perindopril erbumine based on the reaction with dansyl chloride in alkaline medium to give a highly fluorescent derivative which was measured at 496 nm after excitation at 340 nm in dichloromethane. The reaction conditions were studied and optimized. Under the optimum conditions, the fluorescence intensity was linear over a concentration range of 1.0 to 21.0μg/mL ( $R^2=0.9997$ ) with a detection limit of 0.242μg/mL. In order to validate the method, the results were compared with those obtained by a high performance liquid chromatography method. The proposed method was successfully applied to the analysis of perindopril erbumine in pure form and tablets with good precision and accuracy as revealed by t- and F tests. The mechanism of the reaction has also been discussed.<sup>[20]</sup>

A new simple, rapid and sensitive spectrophotometric method was developed for the determination of perindopril in pharmaceutical formulations.

The proposed method is based on thereaction of amine group of drug with 2, 4 dinitrofluorobenzene in dimthylsulfoxide (DMSO) to form yellow colored product, which absorbs maximally at 410 nm.

Beer's law was obeyed in the concentration range 2.5-25 µg/mL with molar absorptivity  $6.71 \times 10^3$  L/mol/cm. The limits of detection and quantitation of the proposed method were 0.17 and 0.52 µg/mL, respectively. The optimum experimental condition for the proposed procedure was investigated. The results of the proposed method were compared with those of Abdellatefs spectrophotometric method, which indicated excellent agreement with acceptable true bias of all samples within  $\pm 2.0\%$ .<sup>[21]</sup>

In another method, the measurement of absorbance at the wavelength of maximum absorptions of Perindopril using water as a solvent was done. The calibration curve was linear in concentration range of 12.5-200 µg/ml for Perindopril with correlation coefficient of 0.9991. The accuracy and precision of the method was determined and validated statically. The method showed good recovery with % RSD less than 2 and good reproducibility. Method was found to be rapid, specific, precise and accurate. This method can be successfully applied for the routine analysis of perindopril. Accuracy of proposed method was confirmed by performing accuracy studies which showed the accepted results. Precision of proposed method was confirmed by performing intraday and inter day precision. The method for the determination of perindopril was validated according to ICH guidelines. Keywords: Perindopril accuracy, linearity, regression equation, precision.<sup>[22]</sup>

*Sharma et al.* has reported a sensitive, selective and well validated Spectrophotometric method using is based on the formation of extractable colored complex of drug with coloring agent Indigo Carmine. Two simple, precise and economical UV methods have been developed for the estimation of Perindopril erbumine in bulk and pharmaceutical formulations. Perindopril erbumine has the Zero order spectroscopic method at 387.2 nm (Method A), Method B applied was Area under Curve (AUC) for analysis of Perindopril erbumine in the wavelength range of 200-400nm. A wavelength maximum was found to be 387.2nm. The concentration range of 5-40 µg ml with linear regression of 0.9996, while the percentage recovery, The LOD and LOQ were 0.32 µg 1 ml and 0.49 µg ml, respectively. The detection and quantitation limits determined were 0.13 and 0.27 mg ml<sup>-1</sup> respectively. The result of analysis have been validated statistically and also by recovery studies. From the percentage recovery and specificity studies it was concluded that there was no interference of common additives during the estimation. This proves the suitability of this method for the routine quality control analysis of the Perindopril erbumine in formulation.<sup>[23]</sup>

*Nafisur et al.* has mentioned two simple, sensitive and accurate spectrophotometric methods have been developed for the analysis of perindopril in pharmaceutical preparations. Method A is based on the formation of ternary complex between zinc(II), eosin and the perindopril, which is extractable with chloroform. The absorption spectrum exhibits a band peaking at 510 nm. Method B is based on the interaction of drug with iodine in dichloromethane resulting in the formation of charge transfer complex which absorbs maximally at 365 nm. Beer's law is obeyed in the concentration range 10–200 µg/ml and 10–180µg/ml with molar absorptivity of  $2.25 \times 10^3$  and  $3.71 \times 10^3$  l/mol·cm for methods A and B, respectively. The detection limits for methods A and B are 0.49 and 0.90µg/ml, respectively. The optimum experimental conditions for the proposed procedures are investigated. Statistical comparison of the results with the reference method shows excellent agreement and indicates no significant difference between the methods compared in terms of accuracy and precision.<sup>[24]</sup>

A new sensitive, simple, rapid and precise two spectrophotometric method has been developed for simultaneous estimation of perindopril and indapamide in pharmaceutical dosage form. This method was based on UVspectrophotometric determination of two drugs, using absorbance correction method. It involves measurement of absorbances at two wavelengths 210.4nm ( $\lambda_{\max}$  of perindopril) and 285.8nm ( $\lambda_{\max}$  of indapamide) in methanol for the simultaneous quantitative determination of perindopril and indapamide in the binary mixture without previous separation. The linearity was observed in the concentration range of 24 – 56 µg mL<sup>-1</sup> for perindopril and 7.5 – 17.5 µg mL<sup>-1</sup> for indapamide. The accuracy and precision of the method was determined and validated statically. The method showed good reproducibility and recovery with % RSD less than 2. Method was found to be rapid, specific, precise and accurate, can be successfully applied for the routine analysis of perindopril and indapamide in bulk, and combined dosage form without any interference by the excipients. The method was validated according to ICH guidelines.<sup>[25]</sup>

A first-order derivative spectrophotometric method for the simultaneous determination of Perindopril erbumine and Indapamide in pharmaceutical dosage forms is described. Methanol was used as a solvent. First order derivative spectroscopy method was adopted to eliminate spectral interference, using 215nm and 241nm zero crossing points for Perindopril Erbumine and Indapamide respectively. The linear dynamic ranges were 1-5µg ml<sup>-1</sup> for Perindopril Erbumine and 2-20µg ml<sup>-1</sup> for Indapamide, the correlation coefficient for the calibration graphs were near to 0.9998, n=5, the precision (%RSD) was better than 1.43% and the

accuracy was satisfactory ( $E_r < 0.99\%$ ). The detection limits were found to be 0.45 and 0.35  $\mu\text{g ml}^{-1}$  for Perindopril Erbumine and Indapamide, respectively. The method was applied in the quality control of commercial tablets and proved to be suitable for rapid and reliable quality control. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method.<sup>[26]</sup>

*Jignesh et al.* has developed and validated an absorption factor method for the simultaneous determination of perindopril erbumine and amlodipine besylate in their combined pharmaceutical formulation dosage form. Absorption factor method was performed for perindopril erbumine and amlodipine besylate at wavelength maxima 215nm and 237 nm respectively. Amlodipine besylate was show liner at 237nm but Amlodipine besylate also showed absorbance at 215nm and give interference in determination of Perindopril erbumine. Quantitative estimation of Perindopril erbumine was carried out by subtracting interference of Amlodipine besylate using experimentally calculated absorption factor. Result of analysis was validated by statistically. The result of the studies showed that the proposed Spectroscopic method is simple, rapid, precise and accurate, which can be used for the routine determination of Perindopril erbumine and Amlodipine besylate in bulk and in its pharmaceutical formulation.<sup>[27]</sup>

#### **DETERMINATION OF PERINDOPRIL BY TLC/HPTLC**

Two specific, sensitive, and precise stability-indicating chromatographic methods have been developed, optimized and validated for determination of perindopril arginin (PER) and amlodipine besylate (AML) in their mixtures and in the presence of their degradation products. The first method was based on thin-layer chromatography (TLC) combined with densitometric determination of the separated bands. Adequate separation was achieved using silica gel 60 F<sub>254</sub> TLC plates and ethyl acetate–methanol–toluene–ammonia solution, 33% (6.5:2:1:0.5 by volume), as a developing system. The second method was based on high-performance liquid chromatography, by which the proposed components were separated on a reversed-phase C<sub>18</sub> analytical column using a mobile phase consisting of phosphate buffer (pH 2.5, 0.01 M)–acetonitrile–tetrahydrofuran (60:40:0.1% by volume) with ultraviolet detection at 218 nm. Different parameters affecting the suggested methods were optimized for maximum separation of the cited components. System suitability parameters of the two developed methods were also tested. The suggested methods were validated in compliance with the ICH guidelines and were successfully applied for the quantification of PER and



AML in their commercial tablets. Both methods were also statistically compared to each other and to the reference methods with no significant differences in performance. [28]

*Varsha et al.* has developed a validated stability indicating HPTLC method for determination Perindopril and Indapamide. The method was based on the separation of two drugs on plates pre-coated with silica gel 60 F<sub>254</sub>. The optimized chromatographic conditions gave compact spot for Perindopril and Indapamide at R<sub>f</sub> value of 0.30 ± 0.02 and 0.60 ± 0.02 respectively. The calibration curve was found to be linear in range of 1000-5000 ng/band and 200-1000 ng/band for perindopril and indapamide respectively. The LOD and LOQ were found to 164 ng/band and 491 ng/band for Perindopril and 41.41 ng/band and 125.49ng/band for Indapamide. The method has been successfully applied to tablets and was validated according to ICH Harmonized Tripartite guidelines using Dichloromethane: Methanol: Glacial acetic acid in the ratio of 9.5:0.5:0.1 v/v/v as mobile phase followed by scanning in absorbance mode at 215 nm. As a new sensitive, simple, rapid and precise high performance thin layer chromatographic (HPTLC) method has been developed and validated for simultaneous determination of Perindopril and Indapamide in pharmaceutical dosage form. The proposed method can be applied for simultaneous determination of Perindopril and Indapamide in bulk and formulation. [29]

#### **OTHER METHODS FOR THE DETERMINATION OF PERINDOPRIL LC-MS/MS**

A high throughput bioanalytical method based on solid phase extraction and liquid chromatography–tandem mass spectrometry (LC–MS/MS), has been developed for the estimation of perindopril and its metabolite perindoprilat, an angiotensin-converting enzyme inhibitor in human plasma. Ramipril was used as internal standard (IS). The extraction of perindopril, perindoprilat and ramipril from the plasma involved treatment with phosphoric acid followed by solid phase extraction (SPE) using hydrophilic lipophilic balance HLB cartridge. The SPE eluate without drying were analyzed by LC–MS/MS, equipped with turbo ion spray (TIS) source, operating in the negative ion and selective reaction monitoring (SRM) acquisition mode to quantify perindopril and perindoprilat in human plasma. The total chromatographic run time was 1.5 min with retention time for perindopril, perindoprilat and ramipril at 0.33, 0.35 and 0.30 min. The developed method was validated in human plasma matrix, with a sensitivity of 0.5ng/ml (CV, 7.67%) for perindopril and 0.3 ng/ml (CV, 4.94%) for perindoprilat. This method was extensively validated for its accuracy, precision, recover,

stability studies and matrix effect especially because the pattern of elution of all the analytes appears as flow injection elution. Sample preparation by this method yielded extremely clean extracts with very good and consistent mean recoveries; 78.29% for perindopril, 76.32% for perindoprilat and 77.72% for IS. The response of the LC–MS/MS method for perindopril and perindoprilat was linear over the range 0.5–350.0 ng/ml for perindopril and 0.3–40 ng/ml for perindoprilat with correlation coefficient,  $r \geq 0.9998$  and  $0.9996$ , respectively. The method was successfully applied for bioequivalence studies in human subjects' samples with 4mg immediate release (IR) formulations.<sup>[30]</sup>

### Gas chromatographic

A capillary gas chromatographic method is described for the determination of perindopril, an anti-hypertensive agent. The method is based on the derivatization of perindopril with pentafluorobenzyl bromide in acetone, using potassium carbonate as a base catalyst. Under a mild condition, the highly polar and nonvolatile perindopril was derivatized into a derivative with suitable chromatographic properties. The resulting derivative was separated on an SE-54 capillary column and detected by a flame-ionization detector. Several parameters affecting the derivatization of perindopril were investigated. The linear range of the method for the determination of perindopril was over 20–300 nmol. The detection limit (signal to noise ratio of 5) of perindopril in 0.2 mL acetone solution was about 3 nmol. Application of the method to the analysis of perindopril in tablets proved to be feasible.<sup>[31]</sup>

### Gas chromatography coupled with mass spectrometry

A gas chromatography mass spectrometry (GCMS) screening procedure was developed for the detection of angiotensin converting enzyme (ACE) inhibitors, their metabolites, and angiotensin (AT) II receptor antagonists in urine as part of a systematic toxicologic analysis procedure for acidic drugs and poisons after extractive methylation. The part of the phase transfer catalyst remaining in the organic phase was removed by solid phase extraction on a diol phase. The compounds were separated by capillary GC and identified by computerized MS in the full scan mode. Using mass chromatography with the ions  $m/z$  157, 160, 172, 192, 204, 220, 234, 248, 249, and 262, the possible presence of ACE inhibitors, their metabolites, and AT II antagonists could be indicated. The identity of positive signals in such mass chromatograms was confirmed by comparison of the peaks underlying full mass spectra with the reference spectra recorded during this study. This method allowed detection of therapeutic concentrations of ACE inhibitors (benazepril, enalapril, perindopril, quinapril,

ramipril, trandolapril, their metabolites, or both) and therapeutic concentrations of the AT II antagonist, valsartan, in human urine samples. Human urine samples were not available for testing cilazapril, moexipril, and losartan; they were detected only in rat urine. The overall recoveries of ACE inhibitors ranged between 80% and 88%, with a coefficient of variation (CV) of less than 10% and the limit of detection of at least 10 ng/ml (signal to noise ratio 3) in the full scan mode. The overall recovery of the valsartan was 68%, with a CV of less than 10%; the limit of detection was at least 10 ng/ml (S/N 3) in the full scan mode.<sup>[32]</sup>

## CONCLUSION

A few methods for determination of perindopril or its metabolites have been reported. Many HPLC assay methods were also used to monitor Perindopril. Methods For the analysis of Perindopril and Perindoprilat has also been reported. Some articles related to the determination of Perindopril alone or in its combination in pharmaceutical dosage forms has been mentioned.

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