Spectroscopy 25 (2011) 123–136
DOI 10.3233/SPE-2011-0502
IOS Press

Quantitative analysis of perindopril erbumine in pharmaceutical preparations by spectrophotometry via ternary complex formation with Zn(II) and eosin and charge transfer complexation with iodine

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Abstract. 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 10–180 μg/ml with molar absorptivity of 2.25×10^3 and 3.71×10^3 l/mol · cm for methods A and B, respectively. The detection limits for methods A and B are 0.49 and 0.90 μg/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.

Keywords: Perindopril erbumine, ternary complex, charge transfer complex, eosin, spectrophotometry

1. Introduction

Perindopril erbumine is chemically known as, tert-butyl-amine salt of [[2S-1-(R, R) 2α, $3\alpha\beta$, $7\alpha\beta$]-1-[2-(1-ethoxy carbonyl butyl)]amino]-oxopropyl, octa-1H indole-2 carboxylic acid [CAS No. 107133-36-8, M.W. 441.6]. It is used for management of hypertension and congestive heart failure. The effectiveness of perindopril as an antihypertensive drug has been demonstrated in various clinical trials [14,17]. The prodrug is transformed *in vivo* by hydrolysis into pharmacologically active perindoprilat. It is thought that perindopril reduces blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increase plasma rennin activity and a decrease in aldosterone. Studies in animals and humans suggest that specific and competitive suppression of the rennin–angiotensin–aldosterone system is the main mechanism by which blood pressure is reduced. The drug is officially listed in the monograph of British Pharmacopoeia [1], which

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describes a potentiometric titration procedure for its assay in formulations. In order to assure the quantity of perindopril in pharmaceutical preparations, several methods have been reported in the literature for the determination of perindopril such as GC [23], GC-MS [24], HPLC [12], capillary electrophoresis [15], atomic absorption spectrophotometry [3] and radioimmunoassay [5,25].

UV-visible spectrophotometry is the technique of choice even today in the laboratories of research, hospitals and pharmaceutical industries due to its low cost and inherent simplicity. The analytical procedures based on spectrophotometry have also been reported for its quantification in commercial dosage forms using bromothymol blue at pH 5 [4], $FeCl_3$ in the presence of potassium thiocyanate [4]. π-acceptors [2] such as 2,3-dichloro-5,6-dicyano-p-benzoquinone, 7,7,8,8-tetracyanoquinodimethane, etracyanoethylene, chloranil and p-chloranilic acid as chromogenic reagents. Kinetic spectrophotometric method was also utilized based on the reaction with 1-chloro-2,4-dinitrobenzene and measuring the rate of change of absorbance at 420 nm [20]. The assay of perindopril was carried out by using zero crossing method [7].

This paper reports two simple, sensitive and accurate spectrophotometric methods for the determination of perindopril in commercial dosage forms. Method A is based on the ternary complex formation with zinc(II) and eosin which is quantitatively extracted into chloroform and measured at 510 nm whereas method B is based on the formation of charge transfer complex between perindopril and iodine in dichloromethane at room temperature.

2. Experimental section

2.1. Apparatus

Spectral runs were made on a Shimadzu UV-visible 1601 spectrophotometer (Kyoto, Tokyo, Japan). All other spectrophotometric measurements were made on Spectronic 20 D^+ spectrophotometer (Milton Roy Company, USA).

2.2. Materials and reagents

All chemicals and reagents were of analytical or pharmaceutical grade. Perindopril erbumine was kindly provided by Glenmark Pharmaceuticals Ltd (Mumbai, India). Pharmaceutical formulations of perindopril erbumine such as Coversyl (Serdia Pharmaceuticals Ltd, India) and Perigard (Glenmark Pharmaceuticals Ltd, Mumbai, India) were purchased from local drug stores.

Zinc sulphate (1.39×10^{-2} M; Sigma Aldrich Chemie, Germany), eosin (1.45×10^{-3} M; Fluka Chemie AG, Switzerland) solutions were prepared in doubly distilled water. Iodine resublimed (2.36×10^{-3} M; Merck Ltd, Mumbai, India) solution was prepared in dichloromethane (Merck Ltd, Mumbai, India).

2.3. Standard test solutions

Standard perindopril (1 mg/ml) (Batch No. K32002003, Glenmark Pharmaceuticals Ltd, Mumbai) solutions were prepared in doubly distilled water and dichloromethane for methods A and B, respectively. The solutions were stable for at least five days if stored at room temperature and dark place.

2.4. Proposed procedures

2.4.1. Method A

Appropriate volumes (0.05–1.00 ml) of the standard perindopril solution (1 mg/ml) were placed into a series of 100 ml separating funnels. To each funnel, 2.2 ml of zinc sulphate (1.39×10^{-2} M) solution was added followed by 2.0 ml of eosin (1.45×10^{-3} M) solution and shaken well. The complex was extracted with 2×2.5 ml portions of chloroform and chloroform layer was passed over anhydrous sodium sulphate. The absorbance of the resulting complex was measured at 510 nm against blank in which the drug is omitted. The nominal content of the drug was determined from the calibration graph or corresponding regression equation.

2.4.2. Method B

Appropriate volumes of standard solution of perindopril (1 mg/ml) corresponding to 50–900 µg were transferred into a series of 5 ml volumetric flasks. To each flask, 2.0 ml of 2.36×10^{-3} M iodine was added and diluted to volume with dichloromethane. The contents of each flask were mixed well and absorbance of the yellow coloured product was measured at 365 nm against a reagent blank in which drug is omitted. The absorbance was plotted against the initial concentration to get the calibration curve. Alternatively, regression equation was derived.

2.5. Procedure for determination of perindopril in pharmaceutical formulations

Twenty five tablets of perindopril (label claim: 2.0 mg/tablet) were powdered and perindopril was extracted separately by shaking with 20 ml doubly distilled water and dichloromethane for methods A and B, respectively, followed by another two extractions, each with 10 ml of distilled water and dichloromethane. The extracts were filtered through Whatmann No. 44 filter paper (Whatmann International Ltd, Kent, UK) into a 50 ml volumetric flask and then diluted to volume with appropriate solvent. An aliquot of the diluted solution was analysed for perindopril content following the proposed procedures.

2.6. Limits of detection and quantitation

According to International Conference on Harmonisation (ICH) guidelines [8], the following expressions are used to evaluate LOD and LOQ:

$$\text{LOD} = 3.3 \times S_0/b \quad \text{and} \quad \text{LOQ} = 10 \times S_0/b,$$

where S_0 and b are standard deviation and slope of the calibration line, respectively.

2.7. Evaluation of bias

The point and interval hypothesis tests [13] have been performed to compare results of the proposed methods with those of the reference method at 95% confidence level. The test method is considered acceptable when its true mean is within ±2.0% of that of the reference method. This can be written as:

$$0.98 < \mu_2/\mu_1 < 1.02$$

which can be generalized to:

$$\theta_{\mathrm{L}} < \mu_2/\mu_1 < \theta_{\mathrm{U}},$$

where θ_{L} and θ_{U} are lower and upper acceptance limits, respectively which were calculated from the following quadratic equation [13]:

$$\theta^2(\overline{x}_1^2 - S_p^2 t^2/n_1) - 2\theta\overline{x}_1\overline{x}_2 + \theta^2(\overline{x}_2^2 - S_p^2 t^2/n_2) = 0.$$

3. Results and discussion

3.1. Method A

Ternary complexes of general formula ($\mathrm{L}_n\mathrm{M}_x\mathrm{S}_y$) have been widely used in spectrophotometric analysis [6,9–11,16,18,19]. In the present study, the ternary complex was utilized for the determination of perindopril in which main ligand L is perindopril, the second ligand S is eosin and M is zinc(II). The ternary complex is extractable with chloroform, whereas the binary system (zinc–drug and zinc–eosin) cannot be extracted in that way. In the ternary complex, the interaction of zinc(II) (X), perindopril (Y) and eosin (Z) may be considered as:

$$\text{either } XY + Z \quad \longleftrightarrow \quad XZ + Y$$
$$\text{or } XY + Z \quad \longleftrightarrow \quad XYZ.$$

The absorption spectra have been recorded for each component, separately, and to their mixture under the experimental conditions discussed above in both aqueous and organic solvent. The spectra revealed (Fig. 1) that aqueous solution of eosin (Z) absorbed maximally in the visible region at 470 nm and there are no significant changes in color and absorption spectrum in the presence of Zn(II) or perindopril, while neither zinc(II) nor the perindopril shows any absorption in the visible region, However, when Zn(II) solution is mixed with a mixture containing perindopril and eosin, the orange–yellow colour changes to red. The absorption spectrum of the reaction mixture exhibited a new band peaking at 510 nm. The later spectrum is attributed to the formation of ternary complex.

3.2. Optimization of the experimental condition

The different experimental parameters affecting the color development and its stability were carefully studied and optimized. Such factors were changed individually while the others were kept constant.

3.2.1. Effect of Zn(II) concentration

The effect of concentration of Zn(II) on the absorbance of the ternary complex was studied over the concentration range 2.78×10^{-4}–6.68×10^{-3} M; keeping the concentrations of the drug (4.53×10^{-4} M) and eosin (5.78×10^{-4} M) constant. It was observed that increasing the concentration of Zn(II) would result in a gradual increase in the absorbance of the ternary complex up to 5.56×10^{-3} M and remained constant up to 6.68×10^{-3} M. Thus 6.12×10^{-3} M of Zn(II) was used as an optimum concentration (Fig. 2).

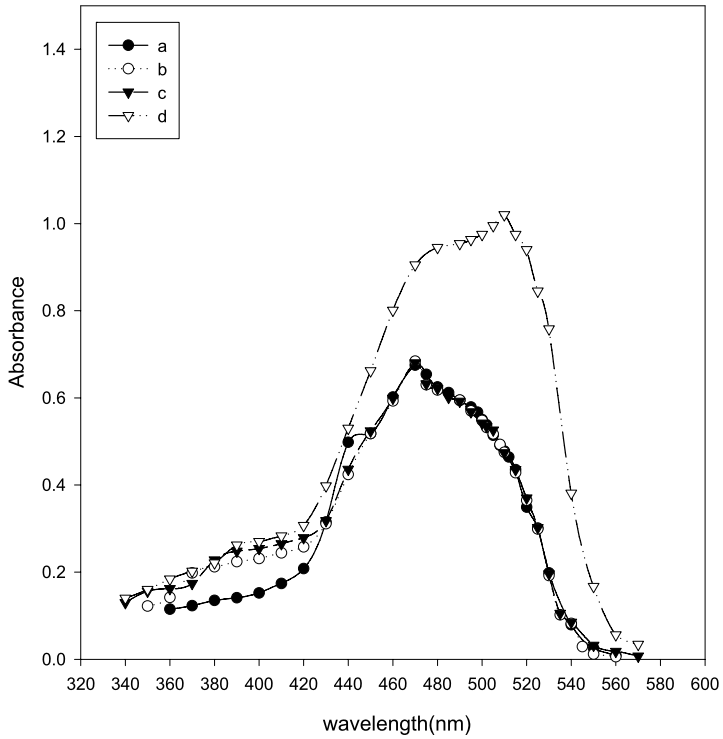


Fig. 1. Absorption spectra of (a) 4.34×10^{-5} M eosin; (b) 4.34×10^{-5} M eosin and 8.35×10^{-4} M Zn^{2+}; (c) 4.34×10^{-5} M eosin and 50.0 μg/ml perindopril against doubly distilled water; (d) 200.0 μg/ml perindopril with 6.12×10^{-3} M Zn^{2+} and 5.78×10^{-4} M eosin extracted into chloroform against blank (6.12×10^{-3} M Zn^{2+} and 5.78×10^{-4} M eosin) treated similarly.

3.2.2. Effect of eosin concentration

The effect of eosin concentration on the absorbance of the ternary complex was examined in the concentration range of 2.89×10^{-5}–6.36×10^{-4} M; keeping the concentration of the drug (4.53×10^{-4} M) and Zn(II) (6.12×10^{-3} M) constant. It was found that increasing the concentration of eosin resulted in a subsequent increase in the absorbance value of the ternary complex up to 5.20×10^{-4} M and remained constant up to 6.36×10^{-4} M. Therefore, a concentration of 5.78×10^{-4} M was used as the optimum concentration of eosin (Fig. 3).

3.2.3. Effect of shaking time

In order to examine the effect of shaking time on the complex formation and the absorbance of the drug–Zn(II)–eosin ternary complex, experiment was performed for the periods ranging from 1–3 min. A constant absorbance was obtained from one min. shaking and remained constant up to three min. Therefore, two min. shaking time was recommended for the determination process.

3.2.4. Stoichiometry of the ternary complex

The stoichiometrty of the reaction was studied adopting the limiting logarithmic method [21]. For this, three sets of experiments were performed. In the first set, the concentration of perindopril was varied; keeping excess concentrations of Zn(II) (6.12×10^{-3} M) and eosin (2.89×10^{-3} M). In the second set, the concentration of Zn(II) was varied while keeping high concentrations of perindopril (4.53×10^{-3} M) and eosin (2.89×10^{-3} M). In the last experiment, excess concentrations of Zn(II) (6.12×10^{-3} M) and perindopril (4.53×10^{-3} M) were employed and the effect on the absorbance was observed on varying

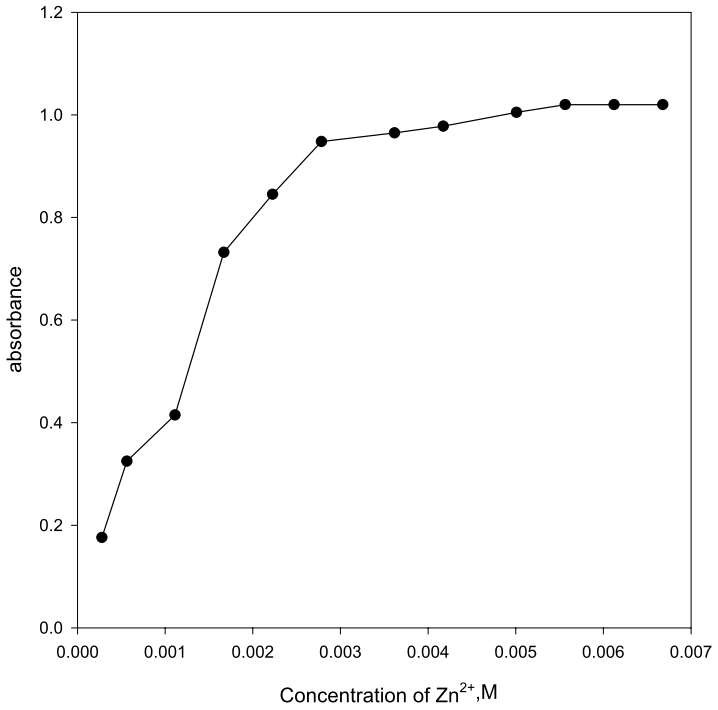


Fig. 2. Effect of molar concentration of Zn^{2+} on the formation of ternary complex.

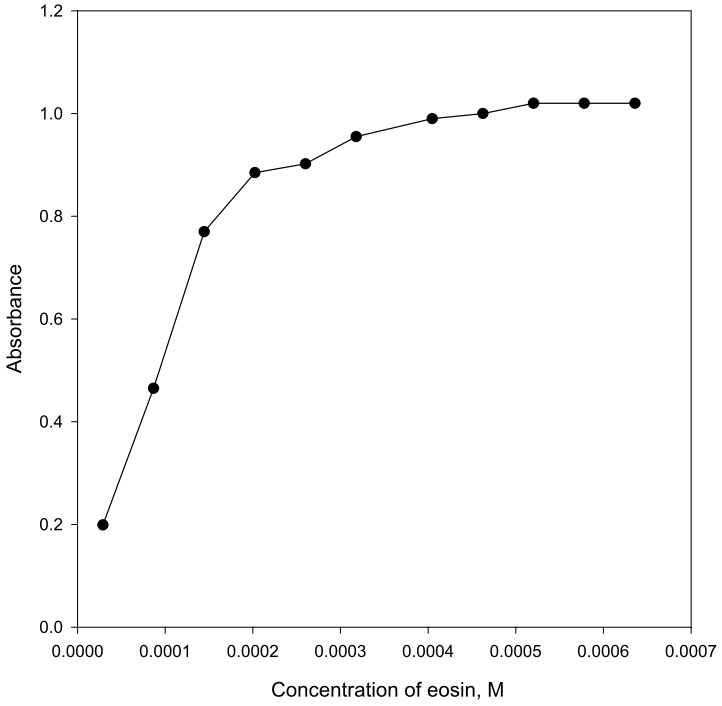


Fig. 3. Effect of molar concentration of eosin on the formation of ternary complex.

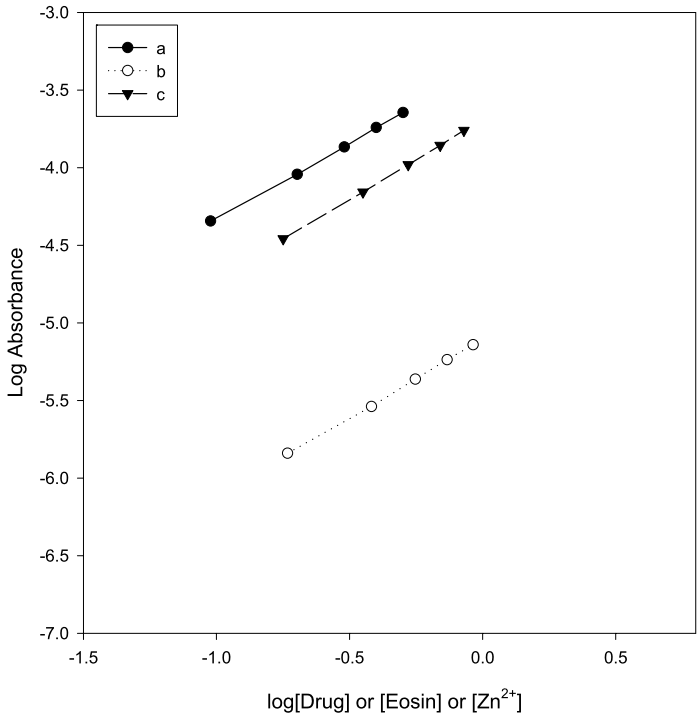


Fig. 4. Limiting logarithmic plot for molar combining ratio between perindopril, Zn^{2+} and eosin: (a) log absorbance vs. log[perindopril]; (b) log absorbance vs. log[Zn^{2+}]; (c) log absorbance vs. log[eosin].

the concentration of eosin. A plot of log absorbance vs. log[perindopril] or log[Zn(II)] or log[eosin] gave straight lines; the values of the slopes are 0.97, 1.02 and 1.01, respectively (Fig. 4(a), (b) and (c)). Hence, it is concluded that the reaction proceeds in the ratio 1:1:1, confirming that one molecule of the drug combines with one molecule of Zn(II) and one molecule of eosin. Based on the obtained molar reactivity, and literature background, the possible reaction pathway is proposed and shown in Scheme 1.

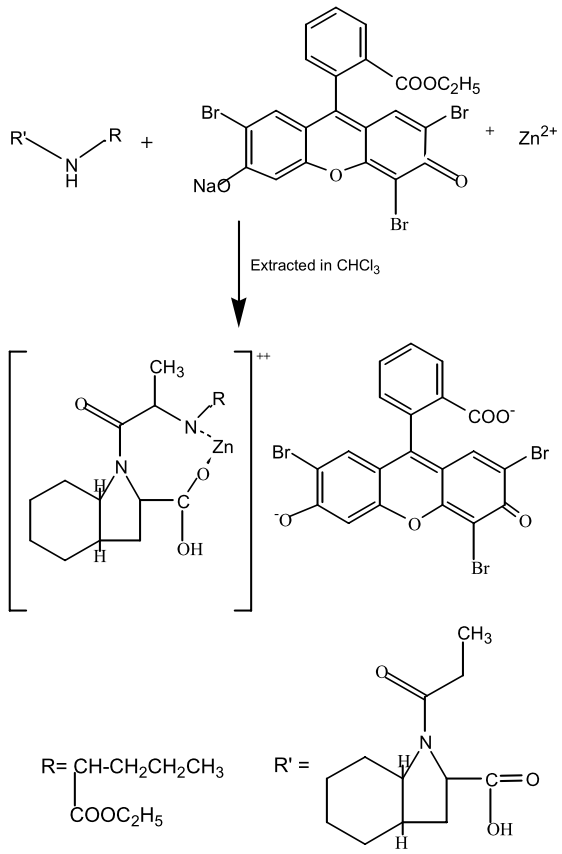
3.3. Method B

The absorption spectrum of iodine in dichloromethane showed only one peak with maximum absorption at 500 nm. The color of iodine changes to yellow upon reaction with perindopril. This is due to charge transfer complexation reaction between the n-donor amine and the σ-acceptor iodine followed by the formation of tri-iodide ion pair (Scheme 2) that exhibited strong absorption maxima at 290 and 365 nm (Fig. 5).

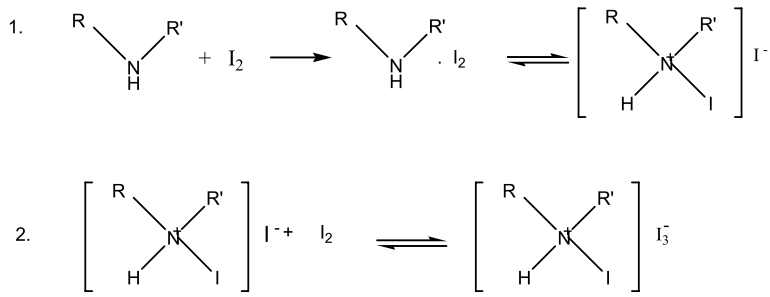
3.4. Optimization of the experimental condition

3.4.1. Effect of concentration of iodine

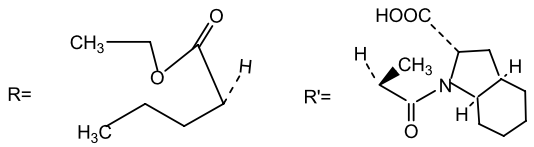
The influence of concentration of iodine was investigated by treating varied concentration (4.73×10^{-5}–1.04×10^{-3} M) of iodine with 0.75 ml of 2.26×10^{-3} M perindopril into a series of 5 ml flasks. The contents were diluted with the same solvent at room temperature. The highest absorbance was achieved with 8.51×10^{-4} M iodine. Further addition of iodine caused no change in the absorbance and



Scheme 1.



Tri- iodide ion pair



Scheme 2.

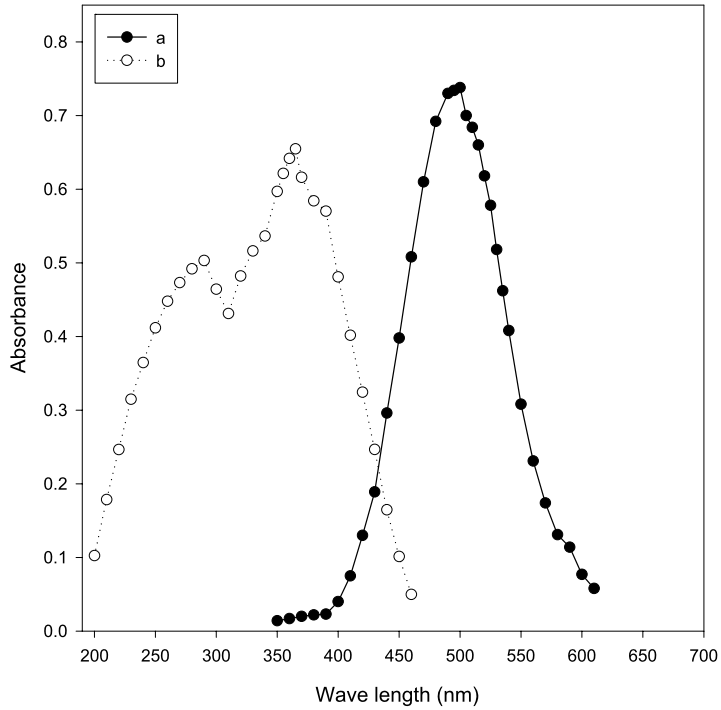


Fig. 5. Absorption spectra of (a) 1.5 ml of 2.364×10^{-3} M iodine in dichloromethane and (b) 750.0 μg perindopril and 2.0 ml of 2.364×10^{-3} M iodine in dichloromethane. In both cases, the solutions were diluted to 5 ml.

therefore, 9.46×10^{-3} M iodine was selected as an optimum concentration for determination process (Fig. 6).

3.4.2. Stoichiometric relationship

Job's method [26] was applied to determine the molar combining ratio for charge transfer complex, perindopril-iodine. It is apparent from Fig. 7 that the molar combining ratio between perindopril and iodine is 1:1. The spectrophotometric data were used to calculate the association constant and apparent molar absorptivity of the perindopril-iodine charge transfer complex using the Ross and Labes equation [22]:

$$\frac{[A][D]}{[A]+[D]} \times \frac{1}{A_\lambda} = \frac{1}{K\varepsilon_\lambda} \times \frac{1}{[A]+[D]} + \frac{1}{\varepsilon_\lambda},$$

where $[A]$ and $[D]$ are the initial molar concentration of iodine and perindopril, respectively. A_λ and ε_λ are the absorbance and apparent molar absorptivity of the charge transfer complex at the wavelength λ. K is the association constant of the complex.

The values of $\frac{[A][D]}{[A]+[D]} \times \frac{1}{A_\lambda}$ were plotted against $\frac{1}{[A]+[D]}$ which yielded a straight line (Fig. 8) with the slope of $\frac{1}{K\varepsilon_\lambda}$ and intercept $\frac{1}{\varepsilon_\lambda}$. This straight line is described by the following regression equation:

$$\frac{[A][D]}{[A]+[D]} \times \frac{1}{A_\lambda} = 7.62 \times 10^{-8} \times \frac{1}{[A]+[D]} + 2.69 \times 10^{-4} \quad (r = 0.9999).$$

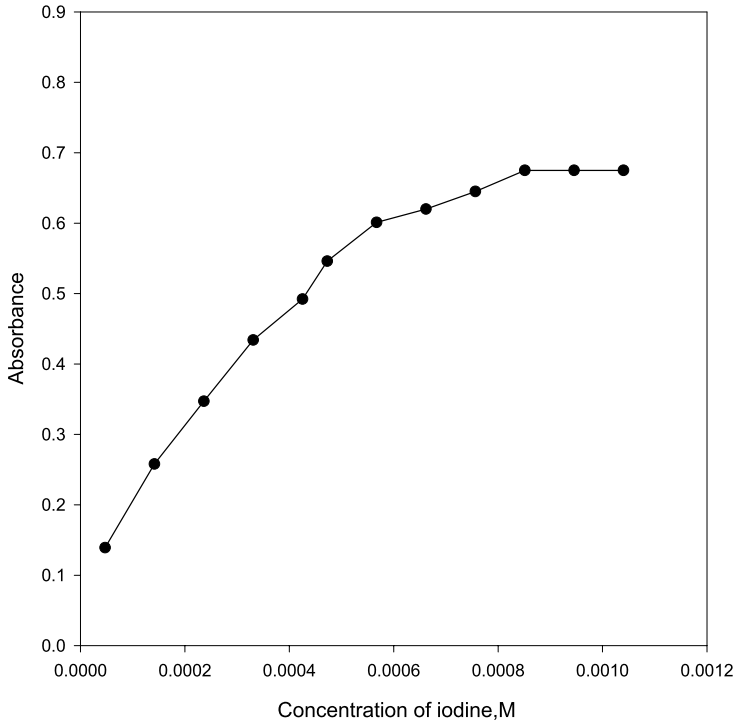


Fig. 6. Effect of the molar concentration of iodine on the absorbance of colored product (perindopril 150.0 μg/ml).

From the above equation, the association constant and apparent molar absorptivity of the charge transfer complex were found to be 3.53×10^3 and 3.71×10^3 l/mol · cm, respectively. The standard free energy of complexation ΔG° was calculated using the relation: $\Delta G^\circ = -RT \ln K$ and found to be -20.25 kJ/mol.

3.5. Validation parameters

3.5.1. Selectivity

The selectivity of the method was ascertained by analyzing standard perindopril in presence of excipients such as lactose, magnesium stearate, cellulose and silicon dioxide. It was observed that both methods are free from interferences.

3.5.2. Analytical data

Standard calibration curves for both the procedures were constructed by plotting absorbance against concentration of perindopril. Beer's law range and molar absorptivity are given in Table 1. Regression equations were derived using the method of least squares. The correlation coefficients, standard deviation of slope and intercept, variance of calibration line and detection and quantitation limits were calculated and listed in Table 1. The values of correlation coefficient and variance clearly indicated the excellent linearity of calibration graph and negligible scattering of the experimental data points around the calibration line, respectively.

3.5.3. Accuracy and precision

In order to determine accuracy and precision of the proposed procedures quality control sample solutions containing three different concentrations (20.0, 100.0 and 180.0 μg/ml) were prepared and analyzed

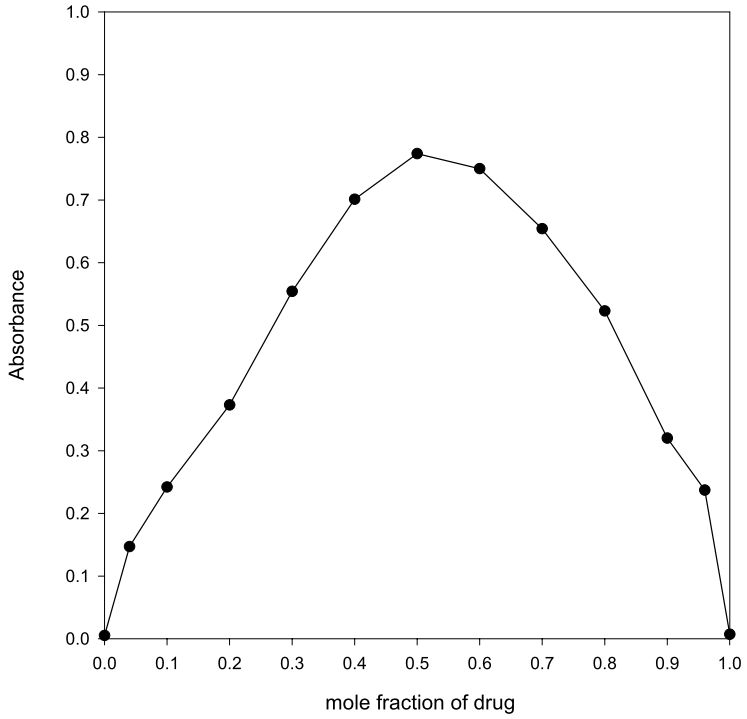


Fig. 7. Job's plot for the reaction between perindopril and iodine in dichlorometane ([Perindopril] = [Iodine] = 1.00×10^{-3} M).

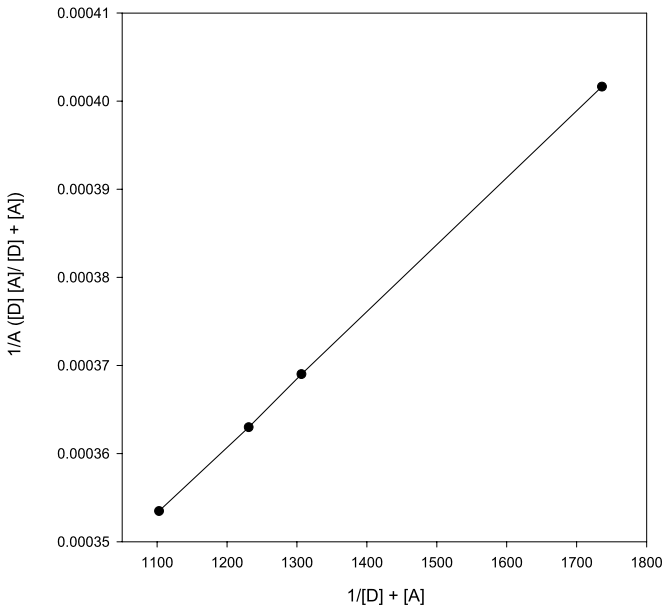


Fig. 8. Plot of $1/A \times ([D][A]/[D] + [A])$ vs. $1/[D] + [A]$.

Table 1
Optical characteristics and statistical data of the regression equations

Parameters	Method A	Method B
Beer's law limit (μg/ml)	10.0–200.0	10.0–180.0
Molar absorptivity (l/mol · cm)	2.25×10^3	3.71×10^3
Linear regression equation	$A = 4.15 \times 10^{-4} + 5.10 \times 10^{-3}C$	$A = -4.43 \times 10^{-4} + 4.50 \times 10^{-3}C$
S_a	4.51×10^{-4}	7.58×10^{-4}
tS_a	1.07×10^{-3}	1.79×10^{-3}
S_b	3.71×10^{-6}	6.93×10^{-6}
tS_b	8.77×10^{-6}	1.64×10^{-5}
Correlation coefficient (r)	0.9999	0.9999
Variance (S_0^2)	2.25×10^{-6}	1.49×10^{-6}
Detection limit (μg/ml)	0.49	0.90
Quantitation limit (μg/ml)	1.48	2.71

Notes: $\pm tS_a$ – confidence limit for intercept; $\pm tS_b$ – confidence limit for slope.

Table 2
Evaluation of the accuracy and precision of the two proposed methods

Proposed methods	Amount (μg/ml) Taken	Found ± SD[a]	Recovery ± RSD[a] (%)	SAE[b]	CL[c]
Method A					
Intra day assay	20.0	19.99 ± 0.22	99.99 ± 1.12	0.10	0.28
	100.0	99.96 ± 0.16	99.96 ± 0.16	0.07	0.20
	180.0	180.04 ± 0.26	100.02 ± 0.15	0.12	0.33
Inter day assay	20.0	19.99 ± 0.33	99.99 ± 1.64	0.15	0.41
	100.0	99.99 ± 0.22	99.99 ± 0.22	0.10	0.28
	180.0	179.88 ± 0.29	99.93 ± 0.16	0.13	0.36
Method B					
Intra day assay	20.0	20.01 ± 0.30	100.05 ± 1.49	0.13	0.37
	100.0	100.05 ± 0.19	100.05 ± 0.19	0.08	0.23
	180.0	179.97 ± 0.34	99.98 ± 0.19	0.15	0.42
Inter day assay	20.0	19.97 ± 0.46	99.83 ± 2.31	0.21	0.57
	100.0	100.01 ± 0.34	100.00 ± 0.34	0.15	0.42
	180.0	180.05 ± 0.43	100.03 ± 0.24	0.19	0.53

Notes: [a]Mean for five independent analyses; [b]standard analytical error; [c]CL, confidence limit at 95% confidence level and four degrees of freedom ($t = 2.776$).

in five replicates within one day as well as for five consecutive days. The standard deviations (SD), relative standard deviations (% RSD), standard analytical error (SAE) and confidence limit (CL) were calculated and summarized in Table 2.

3.5.4. Recovery studies

Recovery experiments were carried out by standard addition method. The concentration of perindopril was determined in tablets (Coversyl-2.0, Perigard-2.0) after spiking with 50 and 200% of additional drug. It was observed from Table 3 that the methods A and B afforded recoveries in the range of 99.972–100.05%, respectively.

Table 3
Determination of perindopril in pharmaceutical preparations by standard addition technique

Pharmaceutical preparations	Method A				Method B			
	Excess of drug added to analyte (%)	Recovery ± RSD (%)[a]	SAE[b]	CL[c]	Excess of drug added to analyte (%)	Recovery ± RSD (%)	SAE[b]	CL[c]
Coversyl-2.0	50.0	99.99 ± 0.15	0.10	0.28	50.0	100.01 ± 0.10	0.05	0.15
(Serdia)	200.0	100.02 ± 0.24	0.16	0.44	200.0	100.05 ± 0.16	0.08	0.23
Perigard-2.0	50.0	100.00 ± 0.20	0.13	0.37	50.0	100.05 ± 0.20	0.11	0.30
(Glenmerck)	200.0	99.972 ± 0.19	0.13	0.36	200.0	100.01 ± 0.17	0.09	0.25

Notes: [a]Mean for five independent analyses; [b]SAE – standard analytical error; [c]CL – confidence limit at 95% confidence level and four degrees of freedom ($t = 2.776$).

Table 4
Determination of perindopril in pharmaceutical preparations by the proposed methods and reference method [2]

Formulations	Method A		Method B		Reference method	
	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)
Coversyl 2.0	99.93	0.101	100.09	0.165	99.92	0.172
(Serdia)	$\theta_L = 0.983$	$\theta_U = 1.016$	$\theta_L = 0.982$	$\theta_U = 1.016$		
	$t = 0.02$	$F = 1.387$	$t = 0.27$	$F = 1.08$		
Perigard 2.0	99.80	0.146	100.02	0.093	99.94	0.201
(Glenmerck)	$\theta_L = 0.983$	$\theta_U = 1.019$	$\theta_L = 0.987$	$\theta_U = 1.011$		
	$t = 0.20$	$F = 1.88$	$t = 0.11$	$F = 1.67$		

4. Application

The applicability of the proposed methods for the assay of perindopril in drug formulations has been tested on commercially available tablets and thus can be extended for the routine quality control analysis of drug in the pharmaceutical industry, hospitals and research laboratories. The results of the proposed methods were statistically compared with those of the reference method [2] using point and interval hypothesis tests. Table 4 shows that the calculated t- (paired) and F-values at 95% confidence level are less than the theoretical ones, confirming no significant difference between the methods compared. For pharmaceutical analysis, a bias of ±2.0% is acceptable and the limit of acceptance interval is within $\theta_L = 0.98$ and $\theta_U = 1.02$. It is observed from the table that the true bias is well within the acceptance limit at 95% confidence level.

Acknowledgements

Authors are thankful to Aligarh Muslim University, Aligarh for providing necessary research facilities. Thanks are extended to Dr. Mubeen Ahmad Khan, Vice President – Analytical Research, Glenmark India Ltd, Mumbai, for providing a gift sample of pure perindopril.

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