

Utility of certain π -acceptors for the spectrophotometric determination of perindopril

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Abstract

Simple, rapid, accurate and sensitive spectrophotometric methods are described for the determination of perindopril. The methods are based on the reaction of this drug as n -electron donor with 2,3-dichloro-5,6-dicyano- p -benzoquinone (DDQ)-7,7,8,8-tetracyanoquinodimethane (TCNQ), tetracyanoethylene (TCNE), chloranil (CL) and p -chloranilic acid (p -CA) as π -acceptors to give highly coloured complex species. The coloured products are measured spectrophotometrically at 588, 843, 419, 550 and 520 nm for DDQ, TCNQ, TCNE, CL and p -CA, respectively, optimization of different experimental conditions is described. Beer's law is obeyed in the range of 20–200 $\mu\text{g ml}^{-1}$ and colours were produced in non-aqueous media and were stable for at least 1 h. Application of the suggested methods to perindopril tablets are presented. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Perindopril, (tert-butylamine salt of 1-(2S)-2-[(1S)-1-carbethoxy-butylamino]-1-oxopropyl(2S, 3aS, 7aS)-perhydroindole-2-carboxylic acid) is an antihypertensive agent whose de-esterified metabolite is an active inhibitor of angiotensin I-converting enzyme (ACE) [2]. The few reported methods in the literature for the determination of perindopril are gas chromatography [3,4] and derivatization-gas chromatography [5].

This paper reports spectrophotometric methods for the assay of perindopril using 2,3-dichloro-5,6-dicyano- p -benzoquinone (DDQ), 7,7,8,8-tetracyanoquinodimethane (TCNQ), tetracyanoethy-

lene (TCNE), chloranil (CL) and p -chloranilic acid (p -CA) as chromogenic reagents. The proposed methods were applied successfully to the determination of perindopril either in pure form or in tablets, with good accuracy and precision.

2. Experimental

2.1. Apparatus

A shimadzu recording spectrophotometer UV 260 was used. with 1-cm quartz cells. Scan speed 40 nm min^{-1} and slit width 2 nm.

2.2. Materials and reagents

Perindopril pure drug and Coversyl tablets (Labelled to contain 4 mg perindopril per tablet) were obtained from Servier Egypt.

Standard stock solution of perindopril, was prepared by dissolving 50 mg of perindopril in 5-ml methanol and the volume to 50-ml was completed by acetonitrile.

DDQ solution, 2 mg ml⁻¹ in acetonitrile. The solution was prepared fresh daily.

TCNQ solution, 1 mg ml⁻¹ in acetonitrile. The solution is stable at least 1 week at 4°C.

TCNE, *p*-CA and CL solutions, 2 mg ml⁻¹ in acetonitrile.

2.3. General procedures and calibration graphs

2.3.1. Method using DDQ

Aliquots of perindopril (containing 0.2–0.6 mg) were transferred into a 10-ml volumetric flask, treated with 1 ml DDQ solution, allowed to stand for 20 min at 20–25°C and diluted to volume with acetonitrile. The absorbance was measured at 588 nm against a reagent blank.

2.3.2. Method using TCNQ:

Aliquots of perindopril (containing 0.2–0.8 mg) were transferred into a 10-ml volumetric flask, treated with 2 ml TCNQ solution, allowed to stand for 50 min at 20–25°C and diluted to volume with acetonitrile. The absorbance was measured at 843 nm against a reagent blank.

2.3.3. Method using TCNE

Aliquots of perindopril (containing 0.4–1.0 mg) were transferred into a 10-ml volumetric flask, treated with 1.5 ml TCNE solution, allowed to stand for 45 min at 20–25°C and diluted to volume with acetonitrile. The absorbance was measured at 464 nm against a reagent blank.

2.3.4. Method using *p*-CA

Aliquots of perindopril (containing 0.2–2.0 mg) were transferred into a 10-ml volumetric flask, treated with 2-ml *p*-CA solution, the volume was completed with acetonitrile and the absorbance was measured at 520 nm against reagent blank.

2.3.5. Method using CL

Aliquots of perindopril (containing 0.5–5.0 mg) were transferred into a 25-ml volumetric flask, treated with 1-ml CL, 10 ml acetonitrile was added, and the flask was allowed to stand at 60°C for 10 min in thermostated water bath. The mixture was cooled and diluted to volume with acetonitrile. The absorbance was measured at 550 nm against a reagent blank.

2.4. Procedure for the assay of the tablets

20 tablets were weighed and an accurately weighed amount of the finely powdered tablets equivalent to 25 mg of perindopril was transferred into a 25-ml volumetric flask, 5 ml methanol was added. The solution was shaken for 5 min to dissolve the drug. The volume was made up to 25-ml with acetonitrile, the solution was filtered and the first few millilitres of the filtrate were discarded. The procedure was continued as mentioned under general procedure and calibration graphs.

2.5. Stoichiometric relationship

Job's method of continuous variation was employed, a 1 × 10⁻³ M standard solution of perindopril and 1 × 10⁻³ M DDQ, TCNQ, TCNE, CL and *p*-CA were used. A series of solutions was prepared in which the total volume of perindopril and reagent was kept at 2 ml (in case of DDQ and TCNQ) and 4 ml (in case of TCNE, CL and *p*-CA). The method was continued as mentioned under the general procedures for the calibration graphs.

3. Results and discussion

3.1. Absorption spectra

π -acceptors, such as tetracyanoethylene (TCNE), 7,7,8,8-tetra-cyanoquinodimethane (TCNQ), chloranil (CL), *p*-chloranilic acid (*p*-CA) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) are known to yield radical ions (formed, in some cases only, presumably via charge-transfer com-

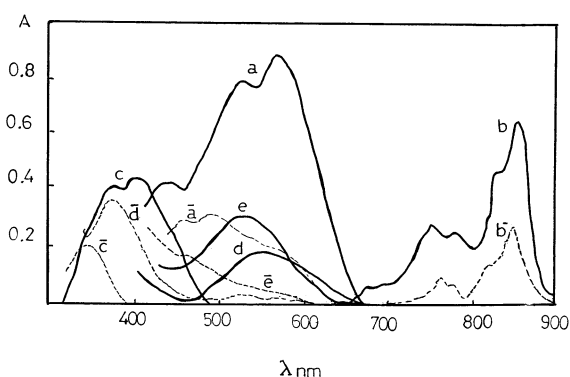


Fig. 1. Absorption spectra for the reaction product of $60 \mu\text{g ml}^{-1}$ perindopril with DDQ (a), TCNQ (b), TCNE (c), CL (d) *p*-CA (e) and the correspondent reagent blanks against acetonitrile \bar{a} , \bar{b} , \bar{c} , \bar{d} and \bar{e} respectively).

plex formation) with a variety of electron donors including amines, iodide ion and metallic salts. This donor–acceptor interaction has been investigated for alkaloids [6] and some pharmaceuticals [7–16] with attention to the analytical application.

The reaction of DDQ with perindopril results in the formation of an intense orange-red product which exhibits three maxima at 588, 547, 450 nm. The 588 nm band, having the highest absorption intensity, was selected for construction of Beer's plot. (Fig. 1).

A solution of perindopril and TCNQ yields an intense blue colour, causing characteristic long-wavelength absorption bands, frequently with numerous vibrational maxima in electronic spectrum (Fig. 1). The predominant chromogen with TCNQ is the blue radical anion $\text{TCNQ}^{\cdot-}$, which was probably formed by the dissociation of an original donor–acceptor (DA) complex with perindopril.

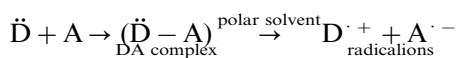


Table 1

Quantitative parameters for the complexation of perindopril with DDQ, TCNQ, TCNE, CL and *p*-CA

Parameters	DDQ	TCNA	TCNE	CL	<i>p</i> -CA
Beer's law limits ($\mu\text{g ml}^{-1}$)	20–60	20–80	40–100	20–200	20–200
Molar absorptivity ($\text{mol}^{-1} \text{cm}^{-1}$)	6201	4432	2861	1137	1883
Slop*	0.0162	0.0116	0.0075	0.0030	0.0049
Intercept*	-0.0288	0.0126	0.0331	0.0137	0.0281
Correlation coefficient*	0.9992	0.9971	0.9995	0.9992	0.9987

* $n = 6$ in all instances.

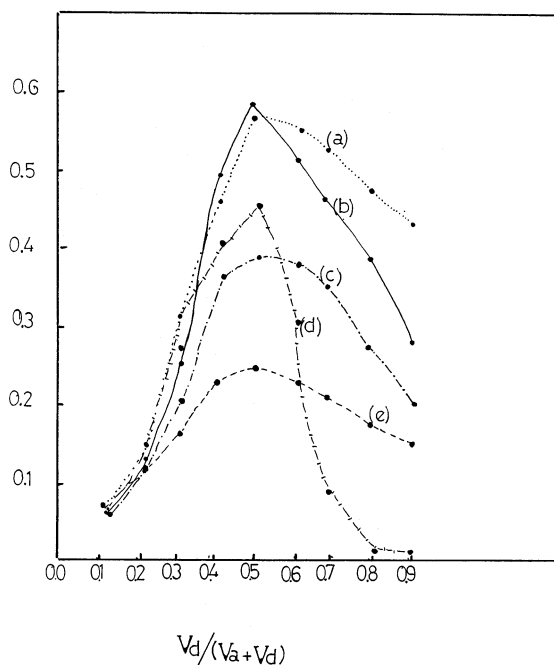


Fig. 2. Continuous variation plot of perindopril (1×10^{-3} M) with 1×10^{-3} M of DDQ (a) and TCNQ (d) (Total volume 2 ml) TCNE (b), *p*-CA (c) and CL (e) (Total volume 4 ml).

The dissociation of DA complex is promoted by the high ionizing power of the solvent, acetonitril [14].

In addition to TCNQ and DDQ radical anions, the reaction of perindopril with TCNE result in the development of yellow complex with 2 maxima at 390 and 419 nm Fig. 1. Also, the reaction of perindopril with halogenated quinones (CL and *p*-CA) results in the development of violet to orange-red solution which exhibit absorption maxima at 550 and 530 nm, respectively (Fig. 1).

Table 2
Statistical analysis of results obtained for Coversyl tablets using the proposed methods

Statistic	DDQ	TCNQ	TCNE	CL	<i>p</i> -CA
Mean % recovery ($P = 0.05$)	100.32	100.83	101.22	99.31	98.38
±S.D.	±0.98	±1.20	±1.03	±0.95	±1.33
<i>N</i>	5	5	5	5	5
Variance	0.96	1.44	1.06	0.90	1.77

3.2. Effect of solvent

As an assay solvent, acetonitrile, benzene, chloroform, ethylene chloride and methylene chloride were examined. Acetonitrile afforded the maximum sensitivity when compared with all other solvent. This is because it possesses the highest dielectric constant of all solvent examined [17], a property which is known to promote the dissociation of the original charge-transfer complexes to the radical ions. Methylene chloride is a possible candidate, although it suffers from its low boiling point which could result in fluctuations of concentration during handling and manipulation. Benzene and chloroform were unsuitable owing to the limited solubility of the reagents [18,19].

3.3. Acceptors sensitivities

The relative sensitivities of the five acceptors can be determined by comparing the molar absorptivities (ϵ) of the chromogen (Table 1). DDQ and TCNQ exhibited the most intense bands. When various concentrations of DDQ, TCNQ, TCNE, CL and *p*-CA were added to a fixed concentration of perindopril, 1 ml of 0.2% w/v solution (for DDQ and CL), 2 ml of 0.1% w/v solution (for TCNQ and *p*-CA) and 1.5 ml of 0.2% w/v solution (for TCNE) were found to be sufficient for production of

maximum and reproducible colour intensity.

3.4. Effect of time (rate of complex formation)

The optimum reaction time was determined by following the colour development at ambient temperature (20–25°C). For reaction with *p*-CA the colour was produced immediately upon mixing the contents of the flask. Complete colour development was attained after 20, 50 and 45 min for DDQ, TCNQ and TCNE, respectively. Whereas for CL complete colour development was attained after 120 min, after heating on water bath at 60°C, for 10–15 min. complete colour development was obtained. The colour remained stable for at least 30 min after dilution with acetonitrile.

3.5. Stoichiometric relationship:

Job's continuous variation graph for the reaction between perindopril and different reagents (Fig. 2) shows that the interaction between these two compounds occurs on an equimolar basis. The reaction of perindopril with DDQ, TCNQ, TCNE, CL or *p*-CA occurs through the formation of a charge-transfer complex (1:1). The coloured reaction product can be represented, taking TCNQ as an example, by the following structure:

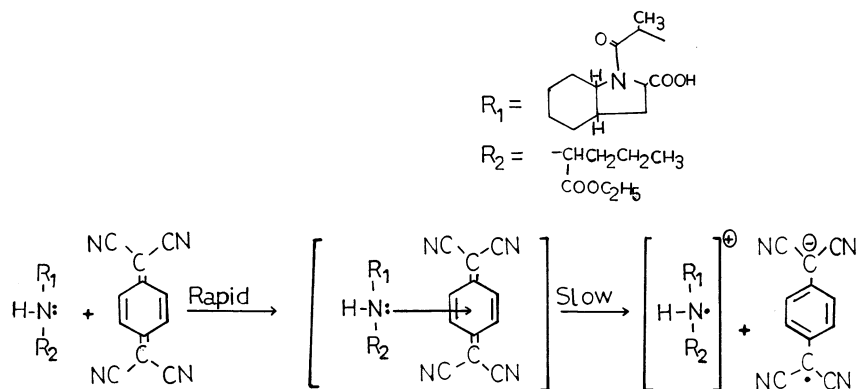


Table 3
Statistical analysis of results obtained using the proposed methods and reference method [1] for analysis of authentic sample

Statistic	Reference method [1]	DDQ	TCNQ	TCNE	CL	<i>p</i> -CA
Mean % recovery ($P = 0.05$)	98.63	99.01	98.93	98.52	99.06	97.99
\pm S.D.	± 0.99	± 0.43	± 0.77	± 0.52	± 0.81	± 0.92
<i>N</i>	5	5	5	5	5	5
Variance	0.98	0.18	0.59	0.27	0.66	0.85
<i>t</i> -test		0.60 (2.31)	0.47 (2.31)	0.17 (2.31)	0.68 (2.31)	1.01 (2.31)
<i>F</i> -test		5.44 (6.39)	1.66 (6.39)	3.63 (6.39)	1.48 (6.39)	0.87 (6.39)

Values in parentheses are the tabulated values of *t* and *F* at $P = 0.05$.

3.6. Quantification, accuracy and precision

The reproducibility and accuracy of the suggested methods were assessed using different concentrations. The validity was checked occasionally during the work by assaying standards. Standard calibration curves for perindopril was prepared by taking series of different concentrations and applying the suggested procedures with DDQ, TCNQ, TCNE, CL and *p*-CA acceptors. Beer's law are valid within microgram concentration range of perindopril (Table 1). The regression equations of these calibration graphs were utilized for determination of unknown concentration of perindopril in tablets. The results obtained were of good accuracy and precision. The applicability of the procedures for estimation of perindopril in tablet were carried out using standard addition technique as a check for accuracy. The produced results were reproducible with low standard deviations (Table 2).

For comparison, the non-aqueous titrimetric method [1] (based on the titration of perindopril dissolved in glacial acetic acid with perchloric acid) was applied. The results agreed well with those of the suggested methods since the calculated *t*- and *F*-values did not exceed the theoretical values (Table 3). The non-aqueous method required high concentration of the drug to permit the titrimetric process, in comparison with the suggested methods which applied successfully for microgram amounts. The methods described are simple and sensitive common excipients found in tablet preparation will not interfere with the methods. The proposed methods can be used as a control methods for production lots.

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