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Determination of captopril in pharmaceutical samples by flow injection analysis

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Abstract: A flow injection spectrophotometric method for the determination of captopril involving measurement of the absorbance of the captopril complex with palladium(II) in a 0.12 M HCl medium at 400 nm is presented. The calibration graph was linear over the range 2×10^{-5}–6×10^{-4} M. The sampling frequency was 90 h^{-1} with sample injections of 70 μl. The proposed method was applied to the determination of captopril in pharmaceutical samples.

Keywords: *Captopril; palladium; flow system; spectrophotometry; pharmaceutical samples.*

Introduction

Captopril, 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline is a drug inhibitor of angiotensin-converting enzyme and has been widely available for the treatment of hypertensive diseases since 1981 [1]. It can be used alone or in combination with thiazide diuretics or digoxin in patients with moderate heart failure [2]. Several methods have been reported for the quantitative determination of captopril including titrimetry [3], electroanalytical [4–7], HPLC [8–13], gas–liquid chromatography [14–16], radioimmunoassay [17–19], fluorimetry [20–22] and spectrophotometry [23–25]. However, the reported procedures are sophisticated and time consuming and thus unsuitable for the analysis of a large number of samples.

An alternative simple chemical procedure for the determination of captopril in pure and in pharmaceutical dosage forms is therefore necessary.

Flow injection analysis (FIA) is an easy and inexpensive way to automate analytical determinations and can be applied in several situations to reduce reagent consumption and increase the repeatability, selectivitiy and accuracy of the determinations. To date, no studies have been carried out on the determination of captopril using flow injection methods.

The aim of this work was to develop a simple and fast method useful for the routine determination of the drug in pharmaceuticals. The procedure proposed here, based on the formation of a complex between captopril and palladium(II), fulfils this requirement and accordingly, this new method using FIA techniques with the peak height as the quantitative parameter is reported.

Experimental

Apparatus

The FIA system consisted of a Gilson HP4 peristaltic pump (Worthington, OH, USA), an Omnifit injection valve (New York, USA) a Hellma 18-μl flow cell (Jamaica, NY, USA) and a Pye Unicam spectrophotometer (Cambridge, UK) as the detector. Connecting tubing of 0.5 mm bore, poly(tetrafluoroethylene) (PTFE) tubing and various end-fittings and connectors (Omnifit) were used.

Reagents

All chemicals were of analytical-reagent grade and the solutions were prepared with doubly distilled water.

Palladium dichloride standard solution (5×10^{-3} M). The palladium dichloride standard solution was prepared by dissolving 0.2216 g of palladium(II) chloride (Merck) in 5 ml of water, to which 0.5 ml of concentrated HCl had been added, and warming the mixture in a water-bath. The solution was cooled and diluted with water in a 250 ml calibrated flask.

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More dilute solutions were obtained by appropriate dilution with water.

Stock captopril solution (1×10^{-3} M). The stock captopril solution was prepared by dissolving 0.0435 g of captopril (Sigma, St Louis, USA) in 200 ml of distilled water, and when not in use was stored at ≃4°C in a dark bottle.

Hydrochloric acid (6 M). This was prepared by dilution of the concentrated acid.

Dosage forms. The composition of the dosage forms studied was as follows. Capoten tablets (Lab. Squibb, SA, Spain): 25 mg captopril and excipient to complete the total weight of the tablet. Dilabar tablets (Lab. Vita, SA, Spain): 50 mg captopril, lactose and other excipient to complete the total weight of the tablet. Ecazide tablets (Lab. Squibb, SA): 50 mg captopril, 25 mg hydrochlorothiazide and excipient to complete the total weight of the tablet. Cesplon-plus (Lab. Dr. Esteve, Spain): 50 mg captopril, 25 mg hydrochlorothiazide, lactose and other excipients to complete the total weight of the tablet. Tensoprel (Lab. Rubio, Spain): 100 mg captopril and excipient to complete the total weight of the tablet.

Synthetic mixtures. Captopril, together with hydrochlorothiazide, combined with common tablet excipients (e.g. starch, glucose, lactose, saccharose, carboxy methyl cellulose and potassium phthallate).

Preparation of standards

An accurately measured volume of the 1×10^{-3} M captopril solution was diluted with water to obtain solutions ranging from 2×10^{-5} M to 6×10^{-4} M.

Preparation of samples

Tablets. The average tablet content weight was calculated from the contents of 20 tablets that were finely powdered and weighed. A portion of this, equivalent to *ca* 25 mg of captopril was accurately weighed and shaken with 20 ml of distilled water for 10 min. The resulting mixture was filtered through a Millipore filter paper and the filtrate diluted with water in a calibrated 100 ml flask. An accurately measured volume (1–3 ml) of this solution was diluted with water in a calibrated 10 ml flask to obtain a solution containing between 3×10^{-5} and 6×10^{-4} M captopril.

Synthetic mixtures. A portion of a thoroughly mixed mixture of each ingredient with different amounts of captopril was accurately weighed, shaken with 20 ml of water for 10 min, and then analysed using the apparatus described above.

Recovery study. An accurately weighed amount of captopril (7–21 mg) for each preparation was added to a 100 ml standard flask containing an accurately weighed quantity of the powdered tablets equivalent to *ca* 8–20 mg of captopril. The contents of the flask were dissolved in distilled water and treated as described for tablets (Table 2).

Recommended procedure for calibration

The FIA manifold (Fig. 1) was used. Seventy microlitres of captopril solution were injected into an inert carrier stream, which then joined the reagent stream, 5×10^{-4} M $PdCl_2$ in 0.12 M HCl, and the peak height was measured at 400 nm. A calibration graph was prepared by plotting the peak height (h) versus captopril concentration over the range 2×10^{-5}–6×10^{-4} M.

Determination of captopril in pharmaceuticals

Suitable aliquots of the pharmaceutical preparations (tablets) described above were analysed by the FIA procedure.

Results and Discussion

Preliminary study of the complex

It is known that, in a neutral or slightly acid solution, palladium(II) ions give coloured complexes with a number of compounds. In acidic solution, however, the reaction is much

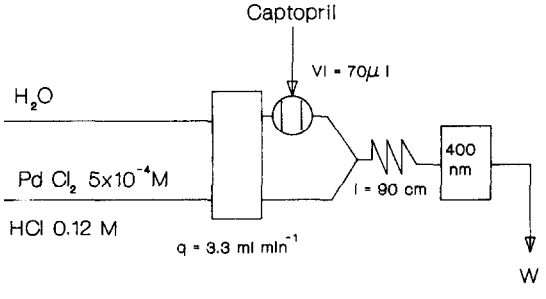

Figure 1
FIA manifolds for the determination of captopril.

more specific for compounds containing sulphur [26]. Of the eight closely related antihypertensive drugs (captopril, enalaripril, lisinapril, ramipril, pentopril, qunapril, zofenopril and fentiapril) only captopril possesses a sulphydryl group [27].

Palladium(II) reacts with captopril to produce a yellow complex with a maximum absorbance in acidic medium at 400 nm. The captopril does not absorb at this wavelength and palladium has a very low absorbance under the same experimental conditions. Therefore, the absorbance measurement was made at 400 nm in all subsequent studies.

Studies carried out in media of different acidity showed that an increase of pH in the range 1–5 had little effect on sensitivity, although the selectivity was better at higher acidity. Therefore, 0.12 M HCl was chosen for the analytical procedure. It was found that the molar ratio of captopril to palladium(II) in the complex was 2:1. The apparent molar absorptivity was 1.6×10^3 l mol cm^{-1}.

The reaction between the palladium(II) and captopril was adopted in order to develop a spectrophotometric–FIA method for determining the drug.

Flow system

The design of the manifold (Fig. 1) is simple. After some preliminary studies, a carrier stream of water was adopted because injection of the sample into the reagent stream led to negative peaks. The reagents and the carrier stream of water were pumped at the same flow rate in order to achieve effective mixing of the sample and reagent solutions. The sample was injected into a water stream, which was then mixed with a stream of palladium(II) chloride dissolved in hydrochloric acid. Palladium(II) formed the captopril–palladium(II) complex and the absorbance was measured in the detector at 400 nm. In the absence of the drug (blank) a very small noise signal was obtained. The presence of the drug caused an increase in the analytical signal, proportional to its concentration.

The sensitivity and sampling rate of captopril determination depended on the sample injection volume (loop size), length and tube diameter of the reactor and flow rate.

Figure 2 shows the effect of the sample injection volume, the reactor length and the flow rate on the peak height. The volume of sample injected was varied from 45 to 135 μl by changing the length of sample loop in the injection valve. The peak heights increased linearly with increasing loop size [Fig. 2(A)]. A loop size of 70 μl was chosen, a sample volume at which a sufficiently good sensitivity was obtained with no excessive waste of sample.

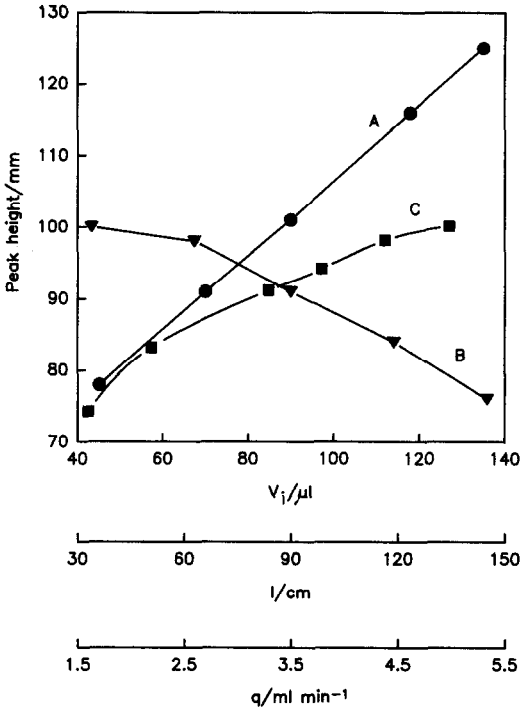

Figure 2
Effect of loop size (A), reactor length (B) and flow rate (C) on the peak height. Sample injected: 4×10^{-4} M captopril.

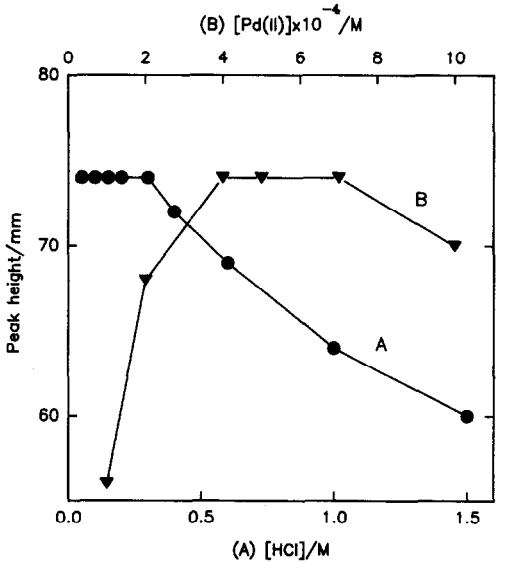

Figure 3
Effect of HCl concentration (A) and palladium(II) concentration (B) on peak height. Sample injected 3.2×10^{-4} M captopril.

The influence of reactor length was studied from the minimum distance possible between the injection valve and detector up to 150 cm. The results [Fig. 3(B)] showed that the peak height decreases as reactor length increases. With short reactors the baseline is unstable and the measurements of peak height are not very reproducible. A 90 cm reactor (inner diameter 0.5 mm) was selected since this provided greatest reproducibility.

The effects of flow rate on peak height were studied over the range 1.5–5 ml min^{-1}. An increase in the flow rate resulted in an increase in analytical signal [Fig. 2(C)]. However, high flow rates also have the effect of decreasing peak measurement reproducibility. A flow rate of 3.3 ml min^{-1} was selected, as a compromise between reproducibility and sampling rate.

This flow system selected provided reasonable sensitivity and a sampling frequency of 90 samples h^{-1}.

Influence of reagent concentration

The influence of HCl and palladium(II) concentration was studied in the range 5.0×10^{-2}–1.5 M and 1.0×10^{-4}–1.0×10^{-3} M, respectively with a fixed concentration of captopril of 3.2×10^{-4} M. As can be observed from Fig. 3, constant and maximum values of peak heights are obtained in concentration ranges of 5.0×10^{-2}–3.0×10^{-1} M [curve 3(A)] and 4.0×10^{-4}–7.0×10^{-4} M [curve 3(B)] for HCl and palladium(II), respectively. Concentrations of 0.12 M HCl and 5.0×10^{-4} M palladium(II) were selected.

Calibration graphs

With the described manifold and under the selected experimental conditions of 5.0×10^{-4} M $PdCl_2$ in 0.12 M HCl, calibration graphs linear between 2.0×10^{-5} and 6.0×10^{-4} M were obtained. The regression equation found was $h = 234.12 \times 10^3$ [captopril] − 2.37, where h is the peak height in mm and the concentrations of captopril are expressed in M, with a correlation coefficient of 0.9992. The precision of the method was tested by analysing 10 replicate samples containing 4.0×10^{-4} M of captopril, the relative standard deviation being ±0.6%. The detection limit (signal to noise ratio = 3) was 2.2×10^{-6} M of captopril. The sampling frequency was 90 samples h^{-1}.

Study of interferents

The influence of commonly used excipients and additives in pharmaceutical dosage forms of captopril was investigated in the determination of 2×10^{-4} M captopril. No interference was observed from the presence of hydrochlorothiazide, lactose, maltose, saccharose, glucose, fructose, phthallate, carboxymethyl-cellulose or starch with the proposed method, even when present in a 25-fold excess.

Applications

The proposed FIA method was applied to the determination of captopril in various pharmaceutical dosage forms. The results obtained and the certified values are summarized in Table 1. As can be seen, there are no significant differences between the certified values and those obtained by the proposed method. In order to evaluate the validity of the proposed method to determine captopril in pharmaceuticals, recovery studies were carried out on samples to which known amounts of captopril had been added. The results are summarized in Table 2. In most cases recovery was higher than 98.9% with a mean recovery higher than 99.7%.

Table 1
Determination of captopril in pharmaceutical preparations

	Captopril content (mg)		
Sample	Found* FIA method	Certified	Recovery (%)
Capoten	24.93 ± 0.27	25	99.7
Dilabar	49.63 ± 0.77	50	99.3
Cesplon-plus	50.03 ± 0.69	50	100.1
Ecazide	49.47 ± 0.75	50	98.9
Tensoprel	100.38 ± 1.07	100	100.4
			Mean ± SD = 99.8 ± 0.7

* Average of 10 determinations ± SD.

Table 2
Recovery of captopril from pharmaceutical preparations

Sample	Captopril (μg ml^{-1}) Initial	Added	Found*	Recovery (%)
Capoten	26.29	65.19	91.26	99.7
	38.67	43.46	82.26	100.3
	50.63	21.73	72.16	99.1
Dilabar	37.59	43.46	80.57	98.9
	49.54	32.59	82.13	100.0
	61.93	21.73	83.59	99.7
Cesplon-plus	36.72	43.46	79.70	98.9
	48.67	32.59	81.10	99.5
	61.49	21.73	83.28	100.3
Ecazide	37.59	43.46	81.48	101.0
	49.76	32.59	81.92	98.7
	61.93	21.73	83.70	100.2
Tensoprel	40.63	43.46	83.65	99.0
	49.98	32.59	82.47	99.7
	59.75	21.73	81.54	100.3
			Mean ± SD =	99.7 ± 0.7

* Average of five determinations.

Conclusions

The proposed FIA method is simple, sensitive, rapid and accurate, compared with many of the reported methods, and can be used for the routine determination of captopril in their dosage forms. Automation of the system can be readily accomplished; all that is needed is the addition of an automatic sampling unit.

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References

[1] K. Florey (Ed.), *Analytical Profiles of Drug Substances*, Vol. 11, pp. 81–136. Academic Press, New York (1982).
[2] A. Goodman, L.S. Goodman, T.W. Rall and F. Murad (Eds), *Las Bases Farmacológicas de la Terapeútica* (7th edn), pp. 616–620. Panamericana, Madrid (1989).
[3] M.E. Mohamed, H.Y. Aboul-Enein and E.A. Gad-Kariem, *Anal. Lett.* **16**, 45–55 (1983).
[4] M.E. Mohamed and H.Y. Aboul-Enein, *Anal. Lett.* **18**, 2591–2603 (1985).
[5] K. Nikolic and K.R. Velasevic, *Pharmazie* **44**, 155–156 (1989).
[6] P. Passamonti, P.V. Bartocci and F. Pucciarelli, *J. Electroanal. Chem. Interfacial Electrochem.* **230**, 99–108 (1987).
[7] K.I. Nikolic and K.R. Velasevic, *J. Pharm. Belg.* **45**, 17–19 (1990).
[8] B. Jarrot, A. Anderson, R. Hooper and W.J. Louis, *J. Pharm. Sci.* **70**, 665–667 (1981).
[9] K. Shimada, M. Tanaka, T. Nambara, Y. Imai, K. Abe and K. Yoshinaga, *J. Chromatogr.* **227**; *Biomed. Appl.* **16**, 445–451 (1982).
[10] K. Hayashi, M. Miyamoto and Y. Sekine, *J. Chromatogr.* **338**, 161–169 (1985).
[11] V. Cavrini, R. Gatti, A.M. Di-Pietra and M.A. Raggi, *Chromatographia* **23**, 680–683 (1987).
[12] C.M. Pereira, Y.K. Tam, R.L. Collins-Nakai and P. Ng, *J. Chromatogr.* **452**, 208–213 (1988).
[13] R. Jain and C.L. Jain, *Indian Drugs* **28**, 380–382 (1991).
[14] O.H. Drummer, B. Jarrott and W.J. Louis, *J. Chromatogr.* **305**, 83–93 (1984).
[15] M.S. Bathala, S.H. Weinstein, F.S. Meeker, S.M. Singhvi and B.H. Migdalof, *J. Pharm. Sci.* **73**, 340–343 (1984).
[16] T. Ito, Y. Matsuki, H. Kurihara and T. Nambara, *J. Chromatogr.* **417**, 79–87 (1987).
[17] J. Tu, E. Lin and E.L. Nickoloff, *Ther. Drug Monit.* **6**, 59–65 (1984).
[18] F.M. Duncan, V.I. Martin, B.C. Williams, E.A.S. Al-Dujaili and C.R.W. Edwards, *Clin. Chim. Acta* **131**, 295–303 (1983).
[19] H. Kinoshita, R. Nakamaru, S. Tanaka, Y. Tohira and M. Sawada, *J. Pharm. Sci.* **75**, 711–713 (1986).
[20] K. Imai, T. Toyoka and Y. Watanabe, *Anal. Biochem.* **128**, 471–473 (1983).
[21] E. Ivashkio, *J. Pharm. Sci.* **73**, 1427–1430 (1984).
[22] V. Cavrini, R. Gatti, P. Roveri and M.R. Cesaroni, *Analyst* **113**, 1447–1452 (1988).
[23] M.A. Raggi, V. Cavrini, A.M. Di Pietra and D. Lacche, *Pharm. Acta. Helv.* **63**, 19–22 (1988).
[24] J. Emmanuel and S.D. Halankar, *Indian Drugs* **26**, 319–320 (1989).
[25] H.T. Askal, *Talanta* **38**, 1115–1158 (1991).
[26] S. Akerfeldt and G. Lovgren, *Anal. Biochem.* **8**, 223–228 (1964).
[27] P. Nuhn, *Pharmazie* **45**, 448–458 (1990).

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