*International Journal of Pharmaceutics*, 86 (1992) 99–106



IJP 02782

**Research Papers**

# Determination of captopril and captopril-hydrochlorothiazide combination in tablets by derivative UV spectrophotometry

I. Panderi and M. Parissi-Poulou

*Department of Pharmacy, University of Athens, Athens (Greece)*

(Received 15 October 1991)
(Modified version received 24 November 1991)
(Accepted 27 January 1992)

*Key words*: Derivative UV spectrophotometry; Captopril; Hydrochlorothiazide; Captopril-hydrochlorothiazide combination tablet

## Summary

Assay procedures based on derivative spectrophotometry have been developed for the determination of captopril alone or in combination with hydrochlorothiazide in tablets. Captopril (5.0–25.0 μg/ml) can be determined by measuring the amplitude of the maximum $D_{2,258\ nm}$ of the second-order derivative spectrum. Combinations of captopril (6.0–14.0 μg/ml) and hydrochlorothiazide (3.0–7.0 μg/ml) in a ratio of 2:1 can be determined using the simultaneous equations method with measurements of the amplitudes of the maximum-minimum of the first-order derivative spectrum $D_{1,278-260\ nm}$ and $D_{1,213\ nm}$. The linearity of the calibration curves was excellent ($r > 0.9997$), the precision (RSD) better than 1.6% and the relative errors ($E_r$) less than 2.6%. The methods were succesfully applied to commercial tablets containing captopril alone or captopril in combination with hydrochlorothiazide.

## Introduction

Captopril (1-(3-mercapto-2-D-methyl-1-oxopropyl)-L-proline (*S,S*)) is an orally active inhibitor of angiotensin-converting enzyme. Its combination with the diuretic hydrochlorothiazide (6-chloro-3,4-dihydro-7-sulfamyl 2H-1,2,4-benzothiadiazine) increases the antihypertensive effects.

A variety of methods have been reported for the quantitative determination of captopril (Shimada et al., 1982; Drummer et al., 1984; Ivashkiv et al., 1984; Pereira and Tam, 1988; Raggi et al., 1988), and captopril-hydrochlorothiazide combination (Kirschbaum and Perlman, 1984) in formulations.

Derivative spectrophotometry is a fast and simple technique which is useful for determining drugs in multicomponent systems or single component formulations in the presence of interfering excipients (Tobias, 1983; Mahrous et al., 1985; Cavrini et al., 1987; Hassan et al., 1987; Abdel-Hamid and Abuirjeie, 1988; Bedair et al., 1988; Di Pietra et al., 1988; Morelli, 1988a–c; Vetuschi et al., 1988; Abdel-Moety et al., 1989; Knochen et

*Correspondence to:* M. Parissi-Poulou, Dept. of Pharmacy, Division of Pharmaceutical Chemistry, Panepistimiopolis, 15771 Zografou, Greece.

al., 1989; Parissi-Poulou et al., 1989; Santoni et al., 1989; Murillo et al., 1990; Corti et al., 1991).

Derivative spectrophotometry has also been applied in the determination of drugs in biological fluids (Fell et al., 1981; Martinez and Gimenez, 1981; Poulou and Macheras, 1986; Fernandez et al., 1988; Green and Hadgraft, 1988; Salinas et al., 1989).

UV derivative spectrophotometry enhances the qualitative features and thus increases the fingerprinting utility of UV spectrophotometry for selective identification and quantification of organic compounds (O'Haver and Green, 1976; O'Haver, 1979).

The technique is based on the principle that, for any given wavelength and concentration interval, the fulfillment of the Lambert-Beer law for the $n$th derivative is governed by the following equation:

$$\frac{d^n A}{d\lambda^n} = \frac{d^n \epsilon}{d\lambda^n} \cdot c \cdot l$$

where $A$ represents the absorbance, $\epsilon$ is the molar absorptivity (l mol$^{-1}$ cm$^{-1}$), $c$ denotes the concentration (mol l$^{-1}$) and $l$ is the pathlength (cm) of the cell.

In this paper, the application of UV derivative spectrophotometry to permit a simple, rapid, accurate and precise assay of captopril (Cap) and captopril-hydrochlorothiazide (Cap-Hy) combination in tablets is described.

## Materials and Methods

*Apparatus and conditions*

A double-beam UV-Vis spectrophotometer (Perkin-Elmer Lambda 7) with the capability of operating in the derivative mode was used. The optimized operating conditions for recording the second-order derivative spectrum ($D_2$) for the determination of Cap and first-order derivative spectrum ($D_1$) for that of the Cap-Hy combination in tablets using 1.000 cm quartz cells, were: scan speed, 120 nm/min; response time, 2 s; spectral slit width, 2 nm; wavelength range, 6 nm.

*Reagents and chemicals*

Methanol was of analytical grade, acetonitrile was far UV and Cap and Hy were obtained from Squibb and used without further purification. Several excipients, used for the interference study, were obtained from commercial sources.

*Standard solutions*

Working standard solutions of Cap (5.0–25.0 $\mu$g/ml) in 0.1 N NaOH were prepared daily from a stock solution of Cap (1.0 mg/ml) in methanol. Working standard solutions of Hy (3.0–7.0 $\mu$g/ml) in 0.01 N HCl and Cap-Hy mixtures at a constant ratio of 2:1 (keeping Cap in the range 6.0–14.0 $\mu$g/ml and Hy in the range 3.0–7.0 $\mu$g/ml) were prepared daily from stock solutions of Cap (1.0 mg/ml) and Hy (0.5 mg/ml) in acetonitrile.

*Sample analysis*

For the determination of Cap the $D_2$ UV spectra of Cap working standard solutions, containing Cap at 5.0–25.0 $\mu$g/ml, were recorded over the 200–280 nm range against a solution in 0.1 N NaOH as blank. The calibration curve was then constructed by plotting the graphically measured (mm) amplitude of the maximum of the $D_{2,258\ nm}$ spectrum vs the corresponding Cap concentration. The following linear equation was obtained through regression analysis of data:

$$h_{2,258\ nm} = 1.34(\pm 0.00096)X - 0.025(\pm 0.1587) \quad (1)$$

$$(r = 0.99997;\ n = 5)$$

where $h_{2,258\ nm}$ is the maximum amplitude (in mm) and $X$ denotes the concentration of Cap (in $\mu$g/ml). This equation was employed in the determination of Cap in formulations.

For the simultaneous determination of Cap-Hy, three calibration curves were constructed as follows: The $D_1$ UV spectra of Hy working standard solutions containing 3.0–7.0 $\mu$g/ml of Hy and mixed Cap-Hy working standard solutions containing 6.0–14.0 $\mu$g/ml of Cap and 3.0–7.0 $\mu$g/ml of Hy at a constant ratio of 2:1 (Cap/Hy)

were recorded over the 200–280 nm range against a solution in 0.01 N HCl as blank.

For the determination of Hy in the presence of Cap, the amplitude $D_{1,278-260\ nm}$ was measured. The following equation was obtained through linear regression analysis of data on standard solutions

$$h'_{278-260\ nm} = 12.99(\pm 0.142)C_{Hy} + 0.6954(\pm 0.62) \quad (2)$$

$(r = 0.9997;\ n = 5)$

where $h'_{278-260\ nm}$ is the maximum-minimum amplitude (in mm) and $C_{Hy}$ the concentration of Hy (in $\mu$g/ml).

For the determination of Cap in the presence of Hy, the amplitude of the maximum of $D_{1,213\ nm}$ ($h'$) of various mixtures was measured. Since both drugs absorb at $D_{1,213\ nm}$, the determination of Cap was achieved by subtracting the value $h'$ from $h'_{213\ nm(Hy)}$ determined for Hy alone. It was found using standard solutions of Hy (3.0–7.0 $\mu$g/ml) that the amplitude $h'_{213\ nm(Hy)}$ at $D_{1,213}$ is linearly related with the Hy concentration:

$$h'_{213\ nm(Hy)} = 9.66(\pm 0.060)C_{Hy} - 0.0633(\pm 0.26) \quad (3)$$

$(r = 0.99994;\ n = 5)$

where $h'_{213\ nm(Hy)}$ is the maximum amplitude (in

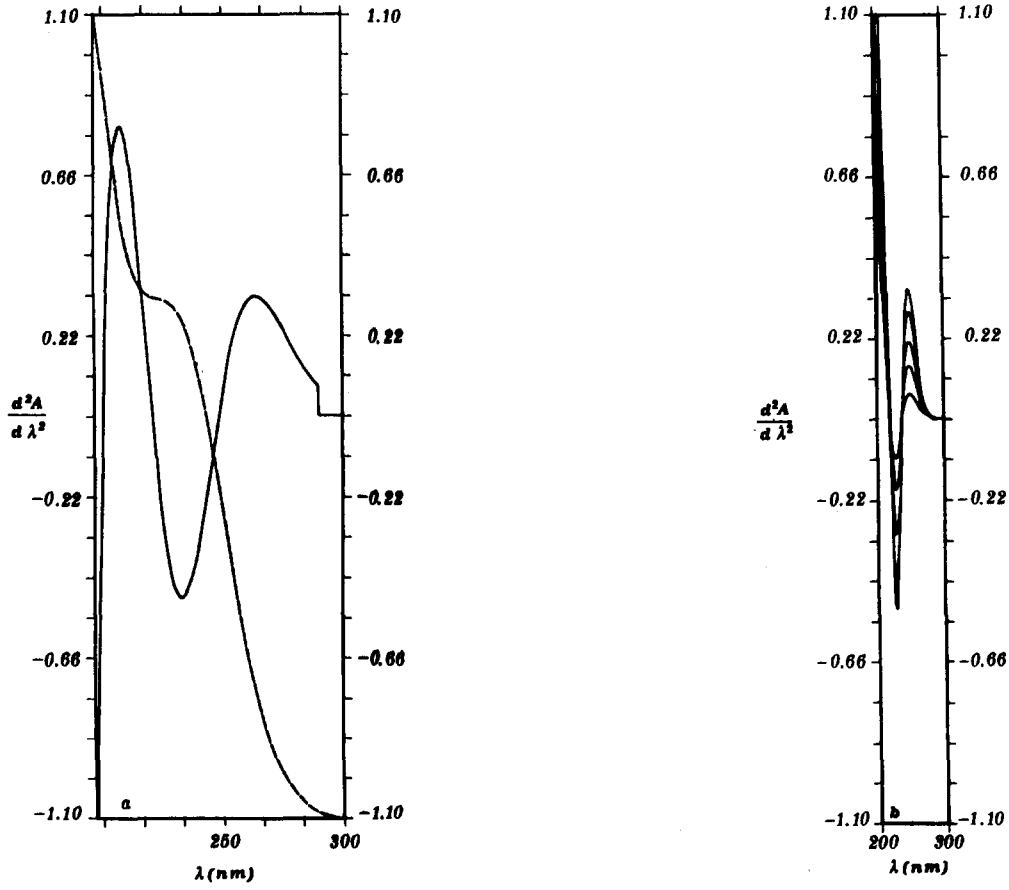


Fig. 1. (a) Zero-order and second-order derivative spectra of captopril. (b) Second-order derivative spectra of captopril (concentration range 5.0–25.0 $\mu$g/ml in 0.1 N NaOH).

mm) at $D_{1,213\ nm}$ produced by Hy alone and $C_{Hy}$ the concentration of Hy (in $\mu$g/ml) previously determined from Eqn 2.

Further, by relating the difference of amplitudes $h'_{213\ nm(Hy)} - h'$, with the Cap concentration, a linear equation was developed for the concentration range utilized:

$$h'_{213\ nm(Hy)} - h' = 3.29(\pm 0.00042)C_{Cap} - 1.18(\pm 0.0036) \quad (4)$$

$(r = 0.9977;\ n = 5)$

where $h'$ is the maximum amplitude (in mm), $h'_{213\ nm(Hy)}$ the maximum amplitude (in mm) (produced by Hy alone) and $C_{Cap}$ the concentration of Cap (in $\mu$g/ml).

From Eqns 2–4, the following expression can be derived:

$$C_{Cap} = 0.2253h'_{278-260\ nm} - 0.303h' + 0.1878 \quad (5)$$

Eqn 5 gives the Cap concentration as a function of the measured amplitudes $h'_{278-260\ nm}$ and $h'$.

*Assay of captopril in tablets*

20 tablets were weighed and pulverized. An accurately weighed amount of powder equivalent to 50 mg of Cap was placed in a 50 ml volumetric flask and about 25 ml of methanol added. The powder was dissolved by placing the flask in an ultrasonic bath for 15 min. The volume was made up to 50 ml with methanol. The solution was filtered, 0.750 ml of the filtrate was placed in a 25 ml volumetric flask and the volume was completed to the mark with 0.1 N NaOH. The amplitude of $D_{2,258\ nm}$ was measured and the Cap content of the tablets was calculated by using the calibration curve (Eqn 1).

*Assay of Cap-Hy combination in tablets*

20 tablets were weighed and pulverized. An accurately weighed amount of powder equivalent to 50 mg of Cap and 25 mg of Hy was placed in a 50 ml volumetric flask and about 25 ml of acetonitrile added. The powder was dissolved by placing the flask in an ultrasonic bath for about 15 min. The volume was made up to 50 ml with acetonitrile. The solution was filtered, 0.120 ml of filtrate was placed in a 10 ml volumetric flask and the volume was complete to the mark with 0.01 N HCl. The $D_1$ spectrum of this solution was recorded, the amplitude $D_{1,278-260\ nm}$ and the maximum $D_{1,213\ nm}$ were measured (mm) and the concentrations of Cap and Hy in tablets were calculated by using Eqns 5 and 2, respectively.

## Results and Discussion

Cap cannot be directly determined by zero-order UV-Vis spectrophotometry, since its zero-order spectrum does not exhibit a distinct absorp-

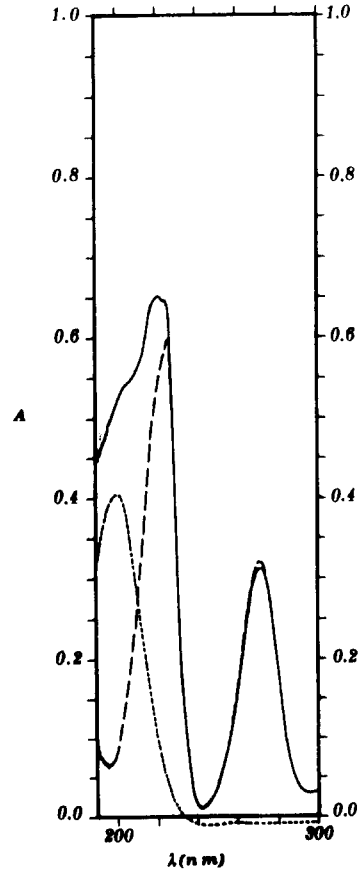


Fig. 2. Zero-order UV spectra of captopril (· · · · · ·), hydrochlorothiazide (- - - - - -) and the binary mixture (———) in 0.1 N HCl.

tion peak. Therefore, in several studies, the determination of Cap in formulations has been carried out using a number of specific reagents in order to produce a derivative that absorbs in the visible region (Raggi et al., 1988). However, this procedure is tedious and time consuming. In view of this, a second-order derivative spectrophotometric method was devised to determine Cap alone in tablets. The amplitude of the maximum at 258 nm of the $D_2$ spectrum was found to be linearly related with Cap concentration in the range 5.0–25.0 $\mu$g/ml, with a least-squares linear-regression equation (Eqn 1).

Ten replicate determinations carried out on a Cap standard solution of 15.0 $\mu$g/ml gave a relative standard deviation (RSD) = 1.00% and a relative error ($E_r$) = −0.73%.

A further comparison of the proposed $D_2$ method vs the USP XXII official procedure (titrimetric method with a solution of 0.1 N $KIO_3$) was carried out by analyzing commercial tablets containing 25 mg of Cap (Capoten). The results gave a mean of 25.00 for the proposed method and a mean of 24.95 ± 0.038 with RSD 0.15% and $E_r$ − 0.1% ($n$ = 5) for the USP official procedure.

Fig. 1 shows (panel a) the zero- and second-order derivative spectra of Cap and (panel b) the second-order derivative spectra of Cap. Fig. 2 illustrates the zero-order UV spectra of Cap, Hy and its binary mixture. Fig. 3 depicts the first-

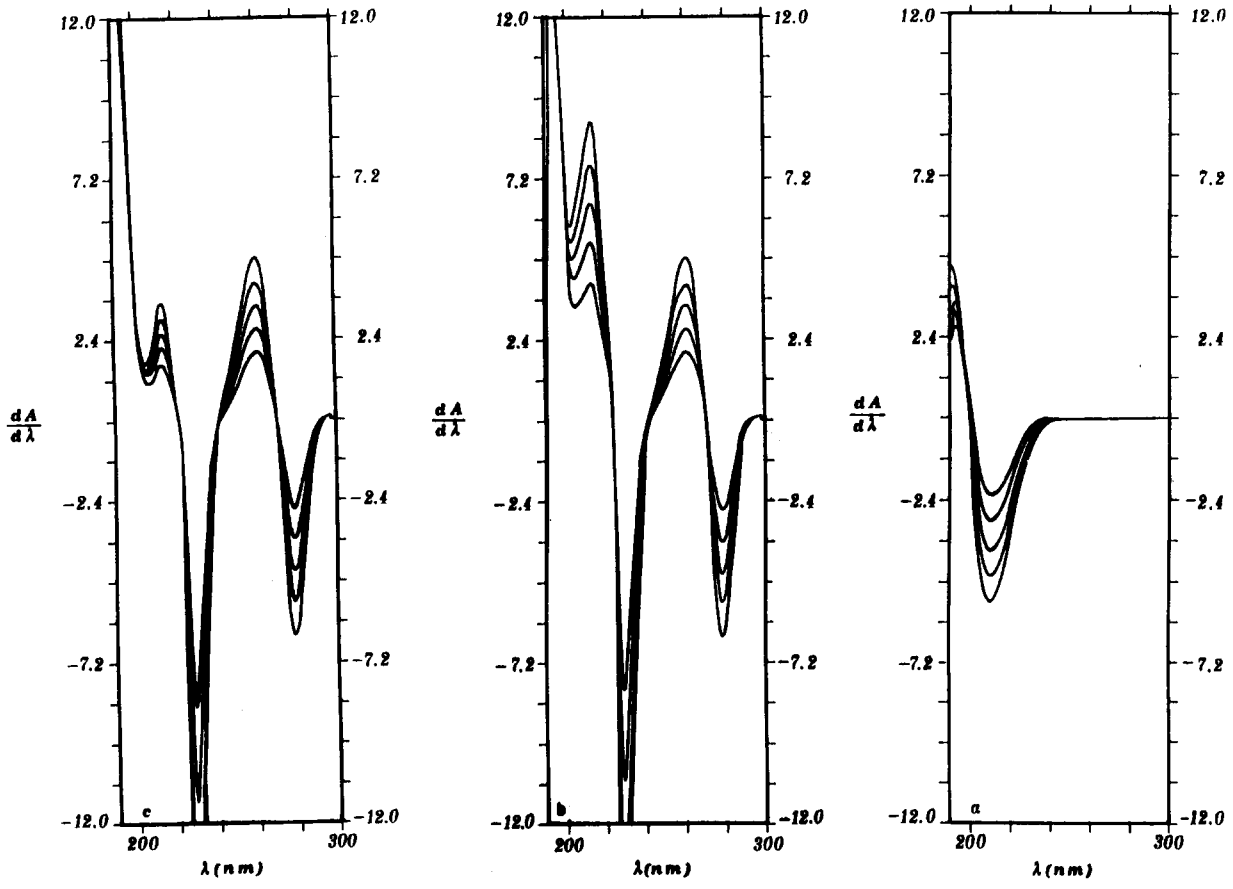


Fig. 3. First-order derivative spectra of (a) captopril (concentration range 6.0–14.0 $\mu$g/ml in 0.1 N HCl), (b) hydrochlorothiazide (concentration range 3.0–7.0 $\mu$g/ml in 0.1 N HCl) and (c) captopril-hydrochlorothiazide mixture in the ratio 2:1 (concentration range 6.0–14.0 $\mu$g/ml for Cap and 3.0–7.0 $\mu$g/ml for Hy in 0.1 N HCl).

order derivative spectra of (a) Cap, (b) Hy and (c) its binary mixture. The $D_1$ spectrum of Hy shows one maximum-minimum pair at 278–260 nm and one maximum at 213 nm which were found to be linearly related with Hy concentration in the range 3.0–7.0 $\mu$g/ml (Eqns 2 and 3). The $D_1$ spectrum of Cap shows one minimum at 213 nm which was found to be linearly related with Cap concentration in the range 6.0–14.0 $\mu$g/ml

$$h_{213\,(\mathrm{Cap})} = 3.43(\pm 0.0227)C_{\mathrm{Cap}} - 0.380(\pm 0.1871)$$

$$(r = 0.9998;\ n = 5)$$

By comparing the $D_1$ spectrum of Hy and Cap, it is clear that the amplitude of $D_{1,278-260\ \mathrm{nm}}$ of Hy is not affected by the presence of Cap, allowing the selective determination of Hy in Cap-Hy mixtures. The amplitude $D_{1,213\ \mathrm{nm}}$ of Cap is affected strongly by the presence of Hy. However, the determination of Cap can be achieved by using a simple relationship which takes into account the contribution deriving from Hy.

10 replicate determinations carried out on a Cap-Hy standard solution of 10.0 $\mu$g/ml of Cap and 5.0 $\mu$g/ml of Hy gave an RSD of 1.69% and $E_r - 0.002$ for Cap and RSD 0.60% and $E_r - 0.026$% for Hy.

The slopes of five calibration curves of Cap and Hy prepared over a period of 5 months had a mean of $3.31 \pm 0.185$ with RSD 5.6% for Cap and a mean of $0.075 \pm 0.0015$ with RSD 2.04% for Hy.

The determination of Cap-Hy combination using first-order derivative spectrophotometry was validated with HPLC (Kirschbaum and Perlman, 1984). The results obtained using both methods are listed in Table 1

TABLE 1

*Determination of Cap-Hy combination in tablets by first-order UV derivative spectroscopy ($D_1$) and HPLC*

| | Cap (mg/tablet) | | Hy (mg/tablet) | |
|---|---|---|---|---|
| | HPLC | $D_1$ | HPLC | $D_1$ |
| Mean ± SD [a] | 49.9 ± 0.52 | 48.66 ± 0.38 | 23.77 ± 0.3 | 24.1 ± 0.43 |
| RSD (%) | 1.049 | 0.79 | 1.26 | 1.78 |
| $E_r$ (%) | −0.002 | −0.047 | −0.049 | −0.036 |

[a] $n = 5$.

TABLE 2

*Effect of tablet additives on second-order derivative determination of Cap*

| Additive | Concentration ratio (additive/Cap) | Recovery (%) ($n = 3$) |
|---|---|---|
| Lactose | 3 | 102.4 |
| Gelatin | 3 | 99.97 |
| Starch | 3 | 101.5 |
| Carbowax [a] | 3 | 101.6 |
| Sodium lauryl sulfate | 2 | 103.2 |
| Magnesium stearate | 1 | 97.47 |
| Carbopol [b] | 2 | 104.93 |
| PVP90 [c] | 2 | 104.00 |
| Hydroxypropylmethyl-cellulose | 2 | 100.8 |
| $PVP_{K30}$ | 2 | 103.26 |

[a] Polyethylene glycol 4000.
[b] Carboxypolymethylene.
[c] Polyvinylpyrrolidone.

In order to examine the effect of common excipients used in the formulation of tablets on the $D_2$ determination of Cap and the $D_1$ determination of Cap-Hy combination, recovery experiments were carried out from synthetic standard solutions in 0.1 N NaOH containing 15.0 $\mu$g/ml of Cap and from synthetic standard solutions in 0.01 N HCl containing 10.0 $\mu$g/ml of Cap and 5.0 $\mu$g/ml of Hy and various excipients in excess.

From the results shown in Tables 2 and 3, it is evident that the determination of Cap and Cap-Hy combination by derivative spectrophotometry does not suffer from spectral interference of the excipients. Thus, the direct determination of Cap and Cap-Hy combination in tablets without isolation of the analyte can be carried out.

The detection limit of Cap alone by $D_2$ spectroscopy was found to be 0.3 $\mu$g/ml, while that of Cap-Hy in mixtures by $D_1$ spectroscopy was determined to be 3.0 $\mu$g/ml for Cap and 1.5 $\mu$g/ml.

The advantages of the two proposed methods $D_2$ for Cap and $D_1$ for Cap-Hy combination in tablets (i.e., short analysis time, unnecessary sample pretreatment and good precision and accuracy) make the procedures suitable for content

TABLE 3

*Effect of tablet additives on first-order derivative determination of captopril-hydrochlorothiazide combination*

| Additive | Concentration ratio | | Recovery (%) [d] | |
|---|---|---|---|---|
| | Additive/ Cap | Additive/ Hy | Cap | Hy |
| Lactose | 2 | 4 | 101.8 | 102.2 |
| Gelatin | 1.5 | 3 | 98.7 | 100.6 |
| Starch | 1 | 2 | 99.7 | 101.4 |
| Carbowax [a] | 2 | 4 | 95.6 | 99.8 |
| Sodium lauryl sulfate | 2 | 4 | 98.4 | 99.26 |
| Magnesium stearate | 0.2 | 0.4 | 98.4 | 99.26 |
| CAHP [b] | 0.2 | 0.4 | 105.1 | 101.2 |
| Carbopol [c] | 2 | 4 | 99.3 | 100.0 |
| Hydroxypropyl-methyl-cellulose | 2 | 4 | 100.0 | 101.93 |

[a] Polyethylene glycol 4000.
[b] Cellulose acetate hydroxyphthalate.
[c] Carboxypolymethylene.
[d] $n = 3$.

uniformity tests, where a great number of assays on individual tablets is required. 20 tablets of Capoten (25 mg of Cap) and 20 tables of Superace (50 mg of Cap and 25 mg of Hy) were analyzed. The results for all tablets gave a mean of $26.28 \pm 0.89$ with an RSD of 3.4% for Cap alone and $48.77 \pm 0.95$ with an RSD of 1.95% for Cap and $25.69 \pm 0.51$ with an RSD of 1.98% for Hy in the fixed combination tablets.

In summary, the proposed analytical procedures based on second-order and first-order UV derivative spectroscopy for the determination of Cap and Cap-Hy combination in tablets offer the advantages of increased resolution and decreased spectral interference and could be used for the rapid and reliable quality control of commercial formulations.

## Acknowledgement

The authors wish to thank Dr P. Macheras for valuable discussions.

## References

Abdel-Hamid, M.e. and Abuirjeie, M.A., Determination of diazepam and oxazepam using high-performance liquid chromatography and fourth-derivative spectrophotometric techniques. *Analyst,* 113 (1988) 1443–1446.

Abdel-Moety, E.M., Abounassif, M.A., Mohamed, M.E. and Knattab, N.A., Spectrophotometric determination of amoxycillin and clavulanic acid in pharmaceutical preparations. *Talanta,* 36 (1989) 683–685.

Bedair, M.M., Korany, M.A. and Issa, A.S., Derivative spectrophotometric determination of clemastine fumarate in pharmaceutical preparations. *Analyst,* 113 (1988) 1137–1138.

Cavrini, V., Di-Pietra, A.M., Raggi, M.A. and Maioli, M.G., Determination of stanozolol in tablets by derivative ultraviolet spectrophotometry and high-performance liquid chromatography. *Analyst,* 112 (1987) 1671–1674.

Corti, P., Aprea, C., Corbini, G., Dreassi, E. and Celesti, L., Derivative resolution in the spectrophotometric assay of pharmaceuticals – Note. IV – Analysis of mixtures of 1,4-benzodiazepine compound. *Pharm. Acta Helv.,* 66 (1991) 50–55.

Di-Pietra, A.M., Cavrini, V., Gatti, R. and Raggi, M.A., Determination of amiodarone hydrochloride in pharmaceutical formulations by derivative UV spectrophotometry and high-performance liquid chromatography (HPLC). *Pharm. Res.,* 5 (1988) 709–712.

Drummer, O.H., Jarrott, B. and Louis, W.J., Combined gas chromatographic-mass spectrometric procedure for the measurement of captopril and sulfur-conjugated metabolites of captopril in plasma and urine. *J. Chromatogr.,* 305 (1984) 83–93.

Fell, A.F., Janvie, D.R. and Stewart, M.J., Analysis of paraquat by second- and fourth-derivative spectroscopy. *Clin. Chem.,* 27 (1981) 286–292.

Fernandez, P., Bermejo, A.M. and Lopez-Rivadulla, M., Application of derivative spectroscopy to the simultaneous identification and determination of plasma amitriptyline and perphenazine. *Anal. Lett.,* 21 (1988) 1045–1054.

Green, P.G. and Hadgraft, J., The use of second-order derivative UV spectroscopy to monitor the percutaneous absorption of naphazoline and oxprenolol. *Int. J. Pharm.,* 46 (1988) 193–198.

Hassan, S.M., Amer, S.M. and Amer, M.M., Determination of fusidic acid and sodium fusidate in pharmaceutical dosage forms by first-derivative ultraviolet spectrophotometry. *Analyst,* 112 (1987) 1459–1461.

Ivashkiv, E., McKinstry, D.N. and Cohen, A.I., Determination of total captopril in human plasma by gas chromatography-mass spectrometry with selected-ion monitoring after reduction of disulfides. *J. Pharm. Sci.* 73 (1984) 1113–1117.

Kirschbaum, J. and Perlman, S., Analysis of captopril and hydrochlorothiazide combination tablet formulations by liquid chromatography. *J. Pharm. Sci.,* 73 (1984) 686–687.

Knochen, M., Altesor, C. and Dol, I., Simultaneous determination of tranylcypromine sulphate and trifluoperazine

dihydrochloride in tablets by first- and fourth-derivative ultraviolet spectrophotometry. *Analyst,* 114 (1989) 1303–1305.

Mahrous, S.M., Abdel-Khalek, M.M. and Abdel-Hamid, M.E., Quantitation of indomethacin, naproxen and ibuprofen in pharmaceutical dosage forms by first and second derivative ultraviolet spectrometry. *J. Assoc. Off. Anal. Chem.,* 68 (1985) 535–539.

Martinez, D. and Gimenez, P., Determination of benzodiazepines by derivative spectroscopy. *J. Anal. Toxicol,* 5 (1981) 10–13.

Morelli, B., First and second derivative spectrophotemetric assay of mixtures of cefuroxime and cephalexin. *J. Pharm. Biomed. Anal.* (1988a) 199–209.

Morelli, B., Determination of mixtures of ampicillin and cloxacillin in pharmaceuticals by second-derivative spectrophotometry, *Anal. Chim. Acta,* 209 (1988b) 175–184.

Morelli, B., Second-derivative spectrophotometric assay of mixture of dicloxacillin sodium and ampicillin sodium in pharmaceuticals. *J. Pharm. Sci.,* 77 (1988c) 1042–1046.

Murillo, J.A., Rodriguez, J., Lemus, J.M. and Alanon, A., Determination of amoxicillin and cephalexin in mixtures by second-derivative spectrophotometry. *Analyst,* 115 (1990) 1117–1119.

O'Haver, T.C., Potential clinical applications of derivative and wavelength modulation spectrometry. *Clin. Chem.,* 25 (1979) 1548–1553.

O'Haver, T.C. and Green, G.L., Numerical error analysis of derivative spectrometry to the quantitative analysis of mixtures, *Anal. Chem.,* 48 (1976) 312–318.

Parissi-Poulou, M., Reizopoulou, V., Koupparis, M. and Macheras, P., Second-derivative UV spectrophotometric determination of hydrochlorothiazide and hydrochlorothiazide-amiloride combination in tablets. *Int. J. Pharm.,* 51 (1989) 169–174.

Pereira, C.M. and Tam, V.K., Simplified determination of Captopril in plasma by high-performance liquid chromatography. *J. Chromatogr.* 425 (1988) 208–213.

Poulou, M. and Macheras, P., Determination of nitrofurantoin in urine. *Int. J. Pharm.,* 3 (1986) 29–34.

Raggi, M.A., Cavrini, V., Di-Pietra, A.M. and Lacche, D., A comparative study of spectrophotometric methods for the determination of captopril in pharmaceutical Formulations. *Pharm. Acta Helv.,* 63 (1988) 19–22.

Salinas, F., Nevado, J.J.B. and Espinosa, A., Determination of oxytetracycline and doxycycline in pharmaceutical compounds, urine and honey by derivative spectrophotometry. *Analyst,* 114 (1989) 1141–1145.

Santoni, G., Mura, P., Pinzauti, S., Gratteri, P. and La Porta, E., Simultaneous determination of naphazoline and diphenhydramine hydrochlorides in nasal drops by second-order derivative UV spectroscopy. *Int. J. Pharm.,* 50 (1989) 75–78.

Shimada, K., Tanaka, M., Nambara, T., Imai, Y., Abe, K. and Yoshinaga, K., Determination of captopril in human blood by high-performance liquid chromatography with electrochemical detection. *J. Chromatogr.* 227 (1982) 445–451.

Tobias, D., First-derivative spectroscopic determination of acetaminophen and sodium salicylate in tablets. *J. Assoc. Off. Anal. Chem.,* 66 (1983) 1450–1454.

Vetuschi, C., Ragno, G. and Mazzeo, P., Determination of *p*-aminosalicylic acid and *m*-aminophenol by derivative UV-spectrophotometry. *J. Pharm. Biomed. Anal.,* 6 (1988) 383–391.