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Notes

Determination of clopamide-pindolol combination in tablets by fourth-order derivative UV spectrophotometry

I. Panderi and M. Parissi-Poulou

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

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Summary

A fourth-derivative spectrophotometric procedure for the simultaneous determination of clopamide and pindolol in binary mixtures, in tablets, is described. Calibration graphs are linear ($r = 0.9999$), the precision (RSD%) better than 2.22 and the percentage relative error (Er%) less than 0.12. No spectral interference from tablet excipients was found. Applications are given for the assay of commercial tablets and content uniformity test. The procedure proved to be suitable for rapid and reliable quality control.

The combination of pindolol and clopamide in tablets is used effectively in the treatment of hypertension. Various methods have been reported for the quantitative determination of pindolol, including HPLC (Shields, 1986; Smith, 1987; Hasegawa.1989), TLC (Jack et al., 1980; Spahn et al., 1985), colorimetry (Mahrous et al., 1986; Zakhari et al., 1989) and GC-MS (Delbeke et al., 1988). Similar procedures such as HPLC (Sane et al., 1986). GC-MS (Stuber et al., 1989) and derivative spectrophotometry (Bedair et al., 1990) have been described for the quantitation of clopamide. However, no method has been reported in the literature concerning the simultaneous determination of the two components clopamide and pindolol, in tablets, as their combination in antihypertensive therapy has become popular during recent years.

The recognised high-resolution potential of derivative spectrophotometry has been used advantageously in pharmaceutical analysis to assay drugs with poorly developed maxima or when excipients or other active ingredients interfere with the conventional spectrophotometric determination (Fasanmade and Fell, 1985; Parissi-Poulou et al. 1989; Morelli, 1990; Panderi and Parissi-Poulou, 1992).

This communication demonstrates how the use of the direct fourth-order derivative (D_4) procedure circumvents the problem of overlapping spectral bands, thus allowing the simultaneous

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

determination of a pindolol-clopamide combination without prior separation. The method yields accurate and reproducible results.

A double-beam UV/Vis spectrophotometer (Perkin-Elmer, Lambda 7) with the capability of derivative mode operation was used. The spectra were recorded in 1-cm matched quartz cells. Suitable settings for recording the fourth-order derivative spectra were: scan speed, 120 nm/min; response time, 2 s; spectral slit width, 2 nm; $\Delta\lambda$, 6 nm; the ordinate minimum and maximum were ± 0.4 for the determination of pindolol and ± 0.05 for that of clopamide.

A series of working standard solutions of clopamide-pindolol mixtures in 0.1 N HCl (containing 40.0 μg/ml of pindolol and increasing amounts of clopamide ranging from 10.0 to 50.0 mg/ml)were prepared daily from stock solutions of clopamide (0.5 mg/ml) and pindolol (1.0 mg/ml) in methanol. Taking appropriate aliquots of these stock solutions, another series of working standard solutions of clopamide/pindolol mixtures in 0.1 N HCl (containing 20.0 μg/ml clopamide and increasing amounts of pindolol ranging from 20.0 to 100.0 μg/ml) were prepared daily.

For the determination of clopamide in the presence of pindolol, the D_4 UV spectra of clopamide-pindolol working standard solutions. containing 40.0 μg/ml pindolol and 10.0–50.0 μg/ml of clopamide were recorded over the 245–280 nm range against a 0.1 N HCl solution as blank. The calibration curve was then constructed by plotting the graphically measured (mm) amplitude of the minimum $D_{4(257\ nm)}$ vs the corresponding clopamide concentration.

Similarly, for the determination of pindolol in the presence of clopamide, the D_4 UV spectra of mixed working standard solutions (containing 20.0 μg/ml of clopamide and increasing amounts of pindolol ranging from 20.0 to 100.0 μg/ml) were recorded against a 0.1 N HCl solution as blank over the 280–310 nm range and the measured (mm) amplitude of the maximum $D_{4(285.6\ nm)}$ was plotted against pindolol concentration to obtain the calibration curve.

Assay of tablets: 20 tablets of Viskaldix (labelled to contain each 10 mg of pindolol and 5 mg of clopamide) were accurately weighed and powdered. A portion of the fine and homogenized powder equivalent to 5 mg clopamide and 10 mg pindolol was accurately weighed and transferred into a 25.0 ml volumetric flask containing approx. 15 ml of methanol. The mixture was sonicated for 1 min, then the volume was brought to 25 ml with methanol and the solution obtained was filtered or centrifuged. 0.5 ml of the resulting clear solution was diluted to 5 ml with 0.1 N HCl. The amplitudes (mm) at 257 and 285.6 nm were graphically measured and the clopamide and pin-

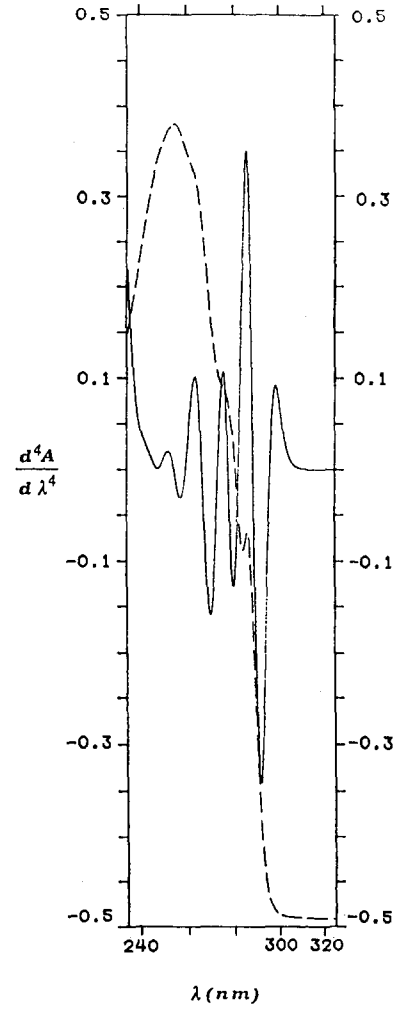

Fig. 1. Absorption (zero-order) UV spectrum (- - - - -) and fourth-order derivative UV spectrum (———), of clopamide (20.0 μg/ml)-pindolol (40.0 μg/ml) mixture in 0.1 N HCl.

dolol concentrations in the sample solution were obtained by interpolating the corresponding calibration curves.

The simultaneous quantitation of clopamide and pindolol in a mixture by conventional UV spectrophotometry cannot be achieved due to the extensive overlap of the spectral bands. When the D_4 spectrum of pindolol-clopamide mixture is recorded (Fig. 1) sharp bands or large amplitudes are produced. This improvement in the characteristic spectral details facilitates the enhancement of accuracy in the quantitative determination of the two compounds. It permits the distinction of slight changes in the spectrum due to small changes in concentration.

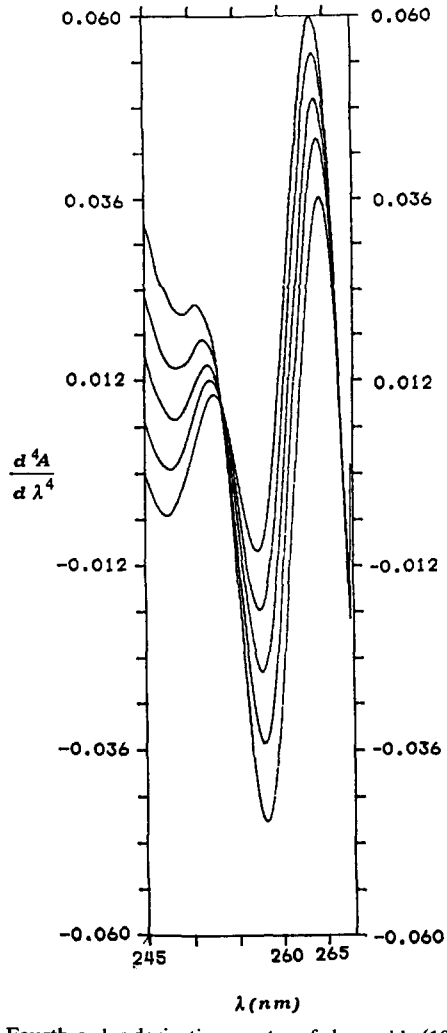

Fig. 2. Fourth-order derivative spectra of clopamide (10.0–50.0 μg/ml) in the presence of pindolol (constant concentration, 40.0 μg/ml).

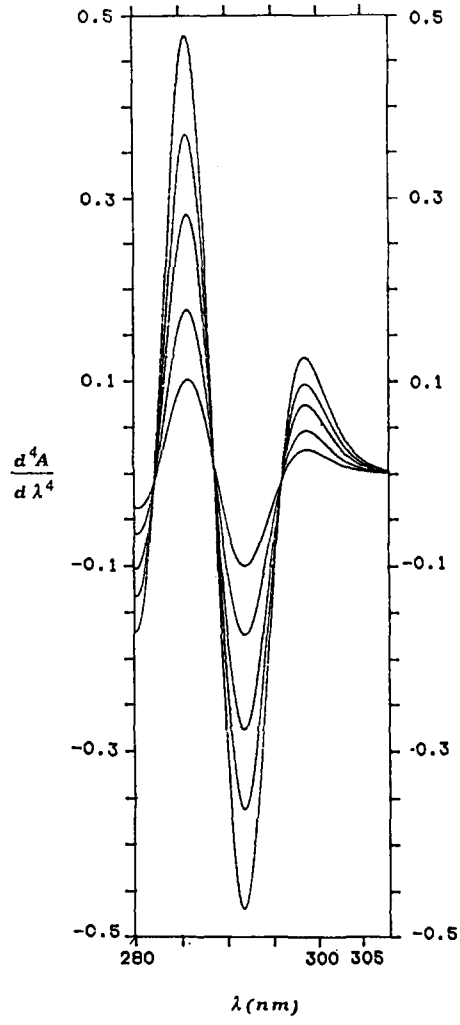

Fig. 3. Fourth-order derivative spectra of pindolol (20.0–100.0 μg/ml) in the presence of clopamide (constant concentration, 20.0 μg/ml).

Fig. 2 shows the D_4 spectra of mixtures containing different concentrations of clopamide (10.0–50.0 μg/ml) in which the pindolol concentration was held constant at 40.0 μg/ml. The amplitude (mm) of the minimum at 257 nm was found to be linearly related to clopamide concen-

tration in the range of 10.0–50.0 μg/ml with a least-squares linear regression equation:

$$D_{4(257\ nm)} = 1.625(\pm 0.012) \times C_{clop} \pm 2.7(\pm 0.3947) \quad (1)$$

$r = 0.99992$, SEE = 0.3763, $n = 5$

where $D_{4(257\ nm)}$ is the minimum at 257 nm. C_{clop} the concentration of clopamide (in μg/ml), r the coefficient of variation and SEE the standard error of estimation.

Similarly, Fig. 3 shows the D_4 spectra of mixtures of different concentrations of pindolol (20.0–100.0 μg/ml) and clopamide (20.0 μg/ml). it was found that the maximum at 285.6 nm is linearly related to pindolol concentration. A typical equation of the least-square linear regression was:

$$D_{4(285.6\ nm)} = 1.1035(\pm 4.31 \times 10^{-3}) \times C_{pin} \pm 3.85(\pm 0.2859)$$

$r = 0.99998$, SEE = 0.2726, $n = 5$

where $D_{4(285.6\ nm)}$ is the maximum at 285.6 nm and C_{pin} the concentration of pindolol (in μg/ml).

The proposed procedure was tested by analysing a standard synthetic solution in 0.1 N HCl containing 20.0 μg/ml clopamide and 40.0 μg/ml pindolol. 10 replicate determinations gave a mean of 19.86 ± 0.41 μg/ml for clopamide with an RSD% = 2.06 and a percentage relative error Er% = −0.7, and for pindolol a mean of 40.05 ± 0.89 μg/ml with RSD% = 2.22 and Er% = 0.12.

In order to examine the effect of common excipients, used in the formulation of tablets, on the D_4 UV spectrophotometric measurements, recovery experiments were carried out from synthetic standard solutions in 0.1 N HCl containing 20.0 μg/ml clopamide 40.0 μg/ml pindolol and various excipients in excess. The data shown in Table 1 indicate that the proposed procedure does not suffer from spectral interference from the excipients.

The detection limit of clopamide-pindolol in the mixture was found to be 2.0 μg/ml for each of the components. The proposed D_4 spectrophotometric method was further evaluated in the assay of commercial tablets (Viskaldix). Assay of tablets with a label claim of 10 mg of pindolol and 5 mg of clopamide yielded recoveries of 95.5–102.2% and 99.2–105.4% of the label claim, respectively, resulting in average percentage label claims (± SD, $n = 7$) of 98.08 ± 2.39 and 102.34 ± 2.53%, respectively.

The method is suitable for the content uniformity test, where a great number of assays on individual tablets is required. 10 individual

TABLE 1

Effect of tablet additives on fourth-order derivative spectrophotometric determination of clopamide-pindolol combination

Additive	Concentration ratio		Recovery (%)	
	Additive/clopamide	Additive/pindolol	Clopamide	Pindolol
Lactose	16	8	101.5	102.3
Gelatin	4	2	103.5	103.8
Starch	16	8	101.7	103.8
Mg stearate	2	1	99.6	100.7
Carbowax [a]	6	3	104.5	104.5
Carbopol	9	4.5	102.5	105.2
CAHP	6	3	98.6	101.2
HPMC [c]	12	6	103.0	104.2
PVP 90 [d]	5	2.5	102.5	104.8

[a] Polyethylene glycol 4000.
[b] Carboxypronylmethylene.
[c] Hydroxypropyl methyl cellulose.
[d] Polyethylene glycol 4000.

Viskaldix tablets were analysed for clopamide and pindolol. All tablets were found to be in the range 99.2–105.4 and 95.5–103.4% of the label claim for clopamide and pindolol. respectively, resulting in average percentage label claims ($\pm$SD, $n = 10$) of 101.13 ± 2.03 and 99.45 ± 2.81%, respectively.

In summary, the proposed analytical procedure based on D_4 spectrophotometry offer the advantages of increased resolution and decreased spectral interference and could be used for the rapid and reliable quality control of commercial formulations containing clopamide and pindolol in binary mixtures.

References

Bedair, M.M., Korany, M.A., Ebdel-Hay, M.A. and Gazy, A.A., Derivative spectrophotometric determination of glibenclamide, mebeverine hydrochloride and clopamide in the presence of their alkaline-induced degradation products. *Analyst*, 115 (1990) 449–553.

Delbeke, F.T., Debackere, M., Desmet, N. and Maertens, F., Qualitative gas chromatographic and gas chromatographic-mass spectrometric screening for β-blockers in urine after solid-phase extraction using extrelut-1 columns. *J. Chromatogr.*, 426 (1988) 194–201.

Fasanmade, A.A. and Fell, A.F., Determination of chlorpromazine and its sulphoxide in pharmaceutical dosage forms by third-order derivative spectroscopy. *Analyst*, 110 (1985) 1117–1124.

Hasegawa, R., Stereoeselective determination of plasma pindolol in endotoxine-pretreated rats by HPLC. *J. Chromatogr.*, 494 (1989) 381–388.

Jack, D.B., Dean. S., Kendall, M.J. and Laugher, S., Detection of some antihypertensive drugs and their metabolites in urine by thin-layer chromatography. *J. Chromatogr.*, 196 (1980) 189–192.

Mahrous, M.S., Issa, A.S., Abdel-Salam, M.A. and Soliman, N., Specrophotometric determination of some cardiovascular drugs using *p*-chloranilic acid. *Anal. Lett.*, 22 (15) (1989) 3011–3024.

Morelli, B., Simultaneous derivative spectrophotometric determination of aztreonam and L-arginine in injections. *J. Pharm. Sci.*, 79 (1990) 261–265.

Panderi, I. and Parissi-Poulou, M., Determination of captopril and captopril-hydrochlorothiazide combination in tablets by derivative UV-spectrophotometry. *Int. J. Pharm.*, 86, (1992), 99–106.

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.

Sane, R.T., Sadana, G.S., Bhounsule, G.J., Gaonkar, M.V., Nadkarni, A.D. and Nayak, V.G., HPLC determination of xipamide and clopamide in pharmaceuticals. *J. Chromatogr.*, 356 (1986) 468–472.

Shields, B.J., Determination of pindolol in human plasma and urine by HPLC with UV detection. *J. Chromatogr.*, 378 (1986) 163–172.

Smith, H.T., High-performance liquid chromatographic method for the determination of pindolol in human plasma. *J. Chromatogr.*, 415 (1987) 93–103.

Spahn, H., Prinoth, M. and Mutschler, E., Determination of pindolol in plasma and urine by thin-layer chromatography. *J. Chromatogr.*, 342 (1985) 458–464.

Stuber, W., Blume, H., Sorgel, F. and Stenzhorn, G., Gas liquid chromatography-mass spectroscopy determination of clopamide in plasma. iJ. Pharm. Sci., 78 (1989) 679–682.

Zakhari, N.A., Hassan, S.M. and El-Shabrawy, Y., Diazotized 4-nitroaniline as a chromogenic reagent for the determination of indole derivatives in certain pharmaceutical preparations. *Anal. Lett.*, 22 (1989) 3011–3024.