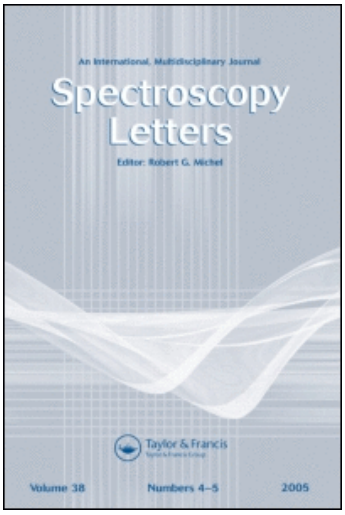

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The Second-Derivative Spectrophotometric Assay of a Multicomponent Analgetic Mixture

Mirjana Medenica[a]; Darko Ivanović[b]; Andjelija Malenović[b]
[a] Department of Physical Chemistry and Instrumental Methods, Faculty of Pharmacy, Belgrade, Yugoslavia [b] Department of Pharmaceutical Chemistry and Drug Analysis, Faculty of Pharmacy, Belgrade

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THE SECOND-DERIVATIVE SPECTROPHOTOMETRIC ASSAY OF A MULTICOMPONENT ANALGETIC MIXTURE

Key words: second-derivative spectrophotometry, zero-crossing method, method with correction, paracetamol, propyphenazone, caffeine

Mirjana Medenica*

Department of Physical Chemistry and Instrumental Methods, Faculty of Pharmacy, Vojvode Stepe 450, 11000 Belgrade, Yugoslavia

Darko Ivanović

Department of Pharmaceutical Chemistry and Drug Analysis, Faculty of Pharmacy, Belgrade

Andjelija Malenović

Department of Pharmaceutical Chemistry and Drug Analysis, Faculty of Pharmacy, Belgrade

ABSTRACT

In this paper the second-derivative spectrophotometric method for the simultaneous determination of some analgetic ingredients was described. Optimal conditions for the quantitative analysis of the three-component analgetic mixture of Dalivon® tablets were settled. The second-derivative order of the spectra in sodium hydroxide with the wavelength modulation was used. For the

* To whom the correspondence should be addressed

determination of paracetamol the "zero-crossing" technique was applied, but for propyphenazone and caffeine the characteristic peak amplitude had to be corrected.

The authors propose this second-derivative spectrophotometry for a rapid, simple, precise and accurate determination of the Dalivon® tablets or a corresponding multicomponent mixture.

INTRODUCTION

The aim of these investigations was to develop a spectrophotometric method for the simultaneous determination of pharmaceutically active ingredients in the Dalivon® tablets. A direct spectrophotometric analysis of drugs in multicomponent dosage forms is often complicated by an interference from the formulation matrix and other active ingredients. The derivative spectroscopy is a simple technique for magnifying the fine structure of spectral curves. It consists of calculating the first, second, or higher order derivative of a spectrum with respect to wavelength or frequency and plotting this derivative rather that the spectrum itself. The higher order derivative spectrophotometry permits to resolve problems of the overlapping bands of the spectra. In a pharmaceutical analysis, an application of the derivative technique for a qualitative and quantitative purpose was first proposed in 1978[1,2].

Numerous techniques for the identification and quantification of our investigated analgetics have been reported in the literature.

Paracetamol was determined in simple pharmaceutical dosage forms using the potentiometric titration[3,4], fluorimetric method[5] and most commonly the classical spectrophotometric method[6-9]. It was determined in a pharmaceutical mixture by voltametric[10], partial least-squares multivariate spectrophotometric[11], differential spectrophotometric method[12], or TLC[13] and HPLC[14]. Paracetamol and its main impurity were analyzed using the second-derivative spectrophotometry[15].

Caffeine was determined spectrophotometrically using a multiple linear regression[16], or first derivations[17]. Most frequently some of separation methods,

such as capillary electrophoresis[18,19], micellar electrokinetic chromatography[20], HPLC[21,22] and HPTLC[23] were used.

Propyphenazone was determined using the first derivative spectrophotometric method[24] and HPLC[25,26].

The multicomponent analgetic mixtures which contained paracetamol, propyphenazone and caffeine were assayed using HPLC[27,28], gas chromatography[29] and densitometric method[30]. In our previous paper[31] we had investigated the possibility to analyze different combinations of drugs by the fourth-derivative spectrophotometry.

EXPERIMENTAL

Apparatus

The Beckman spectrophotometer DU Series 600 with 1 cm quartz cells was used. Suitable settings were: mode $^2D = d^2A/d\lambda^2$, spectrophotometric wavelength range from 200 nm to 350 nm, scan speed 240 nm, wavelength modulation $\Delta\lambda$ = 2 nm and smoothing 25 points.

Materials and Reagents

Dalivon® (250 mg paracetamol, 150 mg propyphenazone and 50 mg caffeine) is the official formulation in the tablet dosage form of *Krka*, Novo Mesto, Slovenia. The USP standard substances of Paracetamol, Propyphenazone and Caffeine were obtained from *Krka*, Novo Mesto. Sodium hydroxide (*Zorka*, Šabac, Yugoslavia) was of analytical reagents grade.

Procedure

Calibration curve

Stock solutions were prepared by dissolving the respective USP standard substance in 0.01 mol/L sodium hydroxide to obtain the concentration of 0.5 mg/mL for paracetamol, 0.15 mg/mL for propyphenazone and 0.1 mg/mL for caffeine. For the calibration curve a series of eight solutions was prepared in the

concentration range from 5.0 to 25.0 μg/mL for paracetamol, from 3.0 to 15.0 μg/mL for propyphenazone and from 1.0 to 5.0 μg/mL for caffeine.

Laboratory mixture

To prove the validity and applicability of the proposed derivative spectrophotometric method, the laboratory mixture of paracetamol, propyphenazone and caffeine was made in the ratio which corresponded to the Dalivon® tablets and measured second-derivative spectra. The stock solution of the laboratory mixture was made by dissolving 25 mg paracetamol, 15 mg propyphenazone and 5 mg caffeine with 0.01 mol/L NaOH in a volumetric flask of 50 mL. For the quantitative analysis of the mixture four series (c = 5 μg/mL, c = 7 μg/mL, c = 10 μg/mL and c = 12 μg/mL calculated to paracetamol) were prepared with ten solutions for each concentration.

Sample

Ten tablets were accurately weighed and finally powdered. The quantity of the powdered tablets, equivalent to the 10-th part of the average mass of one tablet was transferred into a volumetric flask of 50mL. 30 mL 0.01 mol/L NaOH was added and dissolved in an ultrasonic bath for 15 minutes. After 30 min. out of the ultrasonic bath, a volumetric flask was added with 0.01 mol/L NaOH to the mark and after that filtered. That solution contained 25 mg of paracetamol, 15 mg of propyphenazone and 5 mg of caffeine. From that same stock solution four series with ten solutions of each seria was prepared, measuring 0.25, 0.35, 0.50 and 0.60 mL in a volumetric flask of 50 mL adding to the mark 0.01 mol/L NaOH. The second-derivative spectrum was recorded in the range from 200 nm to 350 nm against the 0.01 mol/L NaOH.

RESULTS AND DISCUSSION

The classical spectrophotometric method is not suitable for analyzing a multicomponent mixture because of the overlapping of the absorption spectra of the ingredients. Also, energy changes in molecules are very composite causing wide and complex absorption bands but not too characteristic for identification or

quantification of the substances in a multicomponent mixture. The derivative spectrophotometry is useful for extracting both qualitative and quantitative information from spectral curves of composed or unresolved bands. It permits to resolve the problem of overlapping spectra or to eliminate the interference of the matrix or some other ingredients. Resolution increases with the derivative order. It is the most important to choose the optimal derivative order to resolve the absorption spectra. For a quantitative analysis it is necessary to measure the peak amplitude of the derivative spectra in the concentration range of the Lambert-Beer linearity:

$$\frac{d^n A}{d\lambda^n} = \frac{d^n a}{d\lambda^n} \cdot b \cdot c$$

The zero order, first, second, third and fourth-derivative spectra for all investigated ingredients of the Dalivon® tablets were recorded in the wavelength range from 200 nm to 350 nm. For a simultaneous determination the authors chose the second-derivative order ^2D (Fig. 1.). The signal at 332 nm corresponded to paracetamol, while the signals of caffeine and propyphenazone at that wavelength were zero. That was the reason why the authors chose the "zero crossing" technique for the determination of paracetamol in the combination with propyphenazone and caffeine at that wavelength. But for determining propyphenazone and caffeine it was necessary to correct the peak amplitude. It demanded to calculate the *factor of correction* for both components separately. The factor showed the participation of one component in the mixture with the other when the bands overlapped. It could be calculated from the calibration spectra, because the ratios of the characteristic signals at the chosen wavelength (for example: for paracetamol at λ = 332 nm) and the signals at the wavelength where one of the other components "was zero" (λ = 257 nm) were of constant value. Propyphenazone was determined at 257 nm according to paracetamol, because the signal of caffeine was "zero" at that wavelength. Caffeine was determined at 248 nm according to paracetamol because the signal of propyphenazone was "zero" in the same way calculated with the correction factor using λ = 332nm and λ = 248 nm.

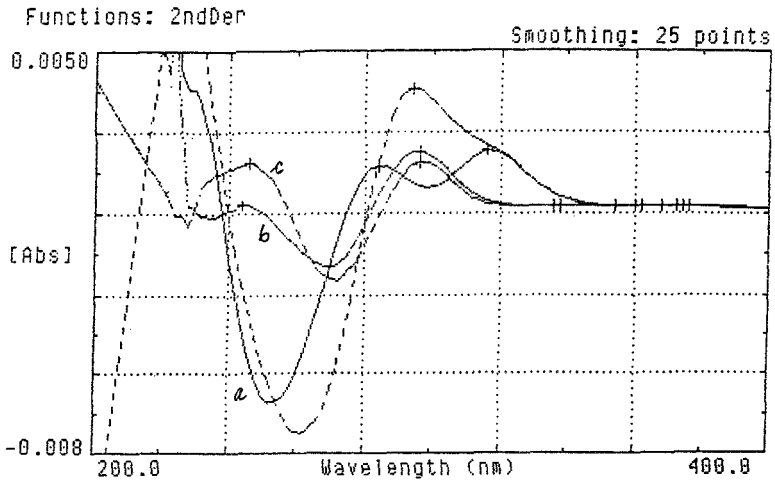

Fig. 1. Second-derivative spectra of: paracetamol (a), propyphenazone (b) and caffeine (c) in the ratio which corresponds to Dalivon® tablets and ^{2}D spectra of Dalivon® tablets (- - -) in 0.01 mol/L NaOH

TABLE 1.

Calibration curves for Dalivon® tablets ingredients

Parameters	Paracetamol (λ = 332 nm)	Propyphenazone (λ = 257 nm)	Caffeine (λ = 248 nm)
Concentration range (μg/mL)	5 – 25	3 – 15	1 – 5
y = ax + b	a = 0.00006 b = 0.000017 r = 0.9992 S_a = 0.000001 S_b = 0.000015	a = 0.0001 b = 0.000088 r = 0.9997 S_a = 0.000001 S_b = 0.000009	a = 0.0006 b = - 0.00011 r = 0.9991 S_a = 0.00001 S_b = 0.000031

TABLE 2.

Determination of laboratory mixture and Dalivon® tablets

Substance	Taken (μg/mL)	Found (μg/mL)	Recovery (%)	CV (%)
LABORATORY MIXTURE				
Paracetamol	5.0	4.9 ± 0.2*	98.0	1.9
	7.0	6.9 ± 0.1	99.3	1.3
	10.0	10.1 ± 0.3	101.0	1.1
	12.0	12.1 ± 0.2	100.8	0.9
Propyphenazone	3.0	3.1 ± 0.1	103.3	2.1
	4.2	4.2 ± 0.2	100.0	2.4
	6.0	6.1 ± 0.1	101.6	1.1
	7.2	7.2 ± 0.2	100.0	1.1
Caffeine	1.0	1.01 ± 0.03	101.0	2.5
	1.4	1.42 ± 0.01	101.4	2.4
	2.0	2.01 ± 0.03	100.5	2.6
	2.4	2.41 ± 0.01	100.4	1.8
DALIVON® TABLETS				
Paracetamol	5.0	4.7 ± 0.2*	94.0	2.5
	7.0	6.78 ± 0.08	96.9	1.2
	10.0	9.89 ± 0.09	98.9	1.6
	12.0	11.7 ± 0.2	97.5	1.7
Propyphenazone	3.0	3.1 ± 0.2	103.4	3.5
	4.2	4.08 ± 0.08	97.2	2.1
	6.0	6.13 ± 0.09	102.2	1.6
	7.2	7.0 ± 0.2	97.3	1.7
Caffeine	1.0	0.98 ± 0.03	98.0	2.9
	1.4	1.44 ± 0.02	102.9	1.3
	2.0	2.00 ± 0.08	100.0	3.9
	2.4	2.34 ± 0.03	97.5	1.1

* Standard deviation (n = 10)

Under described experimental conditions the calibration curves, obtained by plotting ^2D values versus concentration at the mentioned characteristic wavelengths, show linear relationships in the following concentration range: 5-25 μg/mL for paracetamol, 3-15 μg/mL for propyphenazone and 1-5 μg/mL for caffeine. The calibration curves were in agreement with Beer's law. The regression equations for all investigated substances were calculated including the correlation coefficient (r), standard deviation of the slope (S_a) and standard deviation of the intercept (S_b) (Table 1).

For a quantitative analyzing of the Dalivon® tablets four series were prepared with ten solutions in each. Table 2 presents the results of the determination of paracetamol, propyphenazone and caffeine in a laboratory mixture and in the Dalivon® tablets under described experimental conditions.

The mean percentage recoveries and the statistical parameters show a good precision and accuracy of this method.

CONCLUSIONS

The second-derivative order of the spectra of the investigated substances is suitable for a simultaneous determination of the Dalivon® tablets. The proposed second-derivative spectrophotometric method is applicable for a qualitative and quantitative analysis of the Dalivon® tablets. The obtained results are accurate and precise and confirmed by statistical parameters. There was no interference of the excipient in the tablets. The method is simple, rapid, precise and it estimates each drug independently of the other.

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