Arabian Journal of Chemistry (2011) 4, 259–263

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

# Simultaneous determination of ibuprofen and paracetamol using derivatives of the ratio spectra method

**Yousry M. Issa [a], Sayed I.M. Zayed [b,*], Ibrahim H.I. Habib [c]**

[a] *Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt*
[b] *Faculty of Industrial Education, Beni Suef University, Beni Suef, Egypt*
[c] *Microanalytical Chemistry Laboratory, Applied Organic Chemistry Department, National Research Center, Dokki, Cairo, Egypt*

Received 22 June 2010; accepted 23 June 2010
Available online 27 June 2010

**KEYWORDS**

Ibuprofen;
Paracetamol;
Simultaneous determination;
Derivative of the ratio spectra;
Cetofen tablets;
Pharmaceutical formulations

**Abstract** Simple, rapid and accurate new method is described for the simultaneous determination of ibuprofen (IB) and paracetamol (PA) in two components mixture and Cetofen tablets. The method depends on the derivative of the ratio spectra DD by measurement of the amplitude of $^{1}$DD at 225.6 nm and the amplitude of $^{2}$DD at 238.9 nm for IB and PA. Calibration graphs are linear in the range 2–32 (LOD 0.53) and 2–24 (LOD 0.57) μg/ml IB and PA, respectively. The proposed method is successfully applied for simultaneous determining IB and PA in authentic mixtures and Cetofen tablets.



## 1. Introduction

Ibuprofen, 2-(4-isobutylphenyl)-propionic acid [15687-27-1], is non-steroidal anti-inflammatory drug that is available in a variety of preparations. It is commonly used in treatment of pain and inflammation in rheumatoid arthritis and other musculoskeletal disorders (Adams et al., 1976). Paracetamol, acetaminophen [103-90-2], is a very widely used as analgesic and antipyretic drug. Its action is similar to aspirin, and is the most commonly used in pediatrics (Hamm, 2000). Thus, tablets containing ibuprofen and paracetamol showed combined analgesic, anti-inflammatory and antipyretic action. Their chemical structures are shown in Scheme 1.

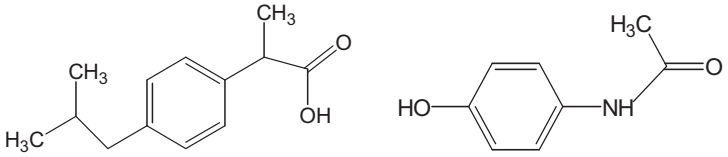
Several methods have been reported for the determination of ibuprofen in pharmaceutical samples and biological fluids, including HPLC (Canaparo et al., 2000; Ravisankar et al., 1998; Vermeulen and Remon, 2000; Teng et al., 2003), gas chromatography–mass spectrometry (Way et al., 1997), capillary electrophoresis (Persson-Stubberud and Astrom, 1999; Hercegova et al., 2000), spectrophotometry (Abdel-Hay et al., 1990; Babu, 1998) and spectrofluorimetry (Hergert and Escandar, 2003; Manzoori and Amjadi, 2003). A literature survey reveals also several methods for assaying paracetamol involving titrimetric (Affalion et al., 1982), flow injection spectrophotometric (Knochen et al., 2003), spectrofluorimetric (Oliva et al., 2005), chemiluminescence (Blazheevsskii and

* Corresponding author. Tel.: +20 2 35676579; fax: +20 2 35728843.
E-mail address: yousrymi@yahoo.com (S.I.M. Zayed).



Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.06.044

Production and hosting by Elsevier




Ibuprofen Paracetamol

**Scheme 1**

Bondarenko, 2004), HPLC (Jiong et al., 2004; Meyer and Karst, 2001), micellar liquid chromatography (Cline Love et al., 1985), voltammetric (Ivaska and Ryan, 1981; Gayal and Singh, 2006), chronoamperometric (Filho et al., 2001), flow injection capillary electrophoresis (Liu et al., 2007). Only two analytical methods with time and chemical-consuming drawbacks have been reported for the determination of IB and PA in their mixtures. These include titrimetry (Parimoo et al., 1989) and HPLC (Hussain et al., 1989). Spectrophotometry is a relatively easy alternative method, which has been applied to determine IB and PA in hyphenated with zero-crossing derivative (Sharaf El-Din et al., 1991) and classical least squares CLS methods (Basu et al., 1998). However, there is a disadvantage associated with these methods. The derivative method causes a decrease in the signal-to-noise ratio as compared with the underlying absorbance band, while CLS is very susceptible to baseline effects since equations assume the response at a wavelength is due entirely to the calibrated constituents. Quantitative spectrophotometry can be improved by derivation of ratio spectra. The advantage of the ratio spectra over the zero-crossing derivatives is direct measuring the amplitudes at maxima or minima enhancing greater sensitivity and selectivity relative to that at zero-crossing points. In this study, ratio derivative spectra method is proposed for the simultaneous determination of ibuprofen and paracetamol in pharmaceutical preparation.

## 2. Experimental

### 2.1. Apparatus

A Shimadzu 1601 double beam UV–Vis spectrophotometer with a fixed slit width (2 nm) connected to an IBM compatible computer and a HP 600 inkjet printer was used. The bundled software was UV PC personal spectroscopy version 3.91 (Shimadzu).

### 2.2. Materials and reagents

Pharmaceutical grade of ibuprofen and paracetamol were kindly supplied by Rameda (6 October City, Egypt), analytical grade methanol (Riedel-dehaen) was used throughout these experiments. The commercial Cetofen tablets used containing 200 mg IB and 325 mg PA per tablet was manufactured by Sigma Company.

### 2.3. Standard solutions

Stock solutions of 1 mg/ml of IB and PA were prepared by dissolving 100 mg of each drug in 100 ml methanol. The standard solutions were prepared by dilution of the stock solutions with the same solvent to reach concentration range 2–32 and 2–24 μg/ml for IB and PA.

### 2.4. Procedure

#### 2.4.1. $^{1}$DD method for IB

The UV absorption spectra of the solutions prepared at different concentrations (2–32 μg/ml) in its binary mixture with PA were recorded against methanol and, smoothed at $\Delta\lambda = 2$ nm then divided by the smoothed at $\Delta\lambda = 2$ nm spectrum of the standard solution of PA (20 μg/ml in methanol), the ratio spectra were obtained. The first derivative was calculated for the obtained spectra with $\Delta\lambda = 4$ nm. The amplitudes at 225.6 nm were measured and found to be proportional to the concentration of IB.

#### 2.4.2. $^{2}$DD method for PA

The UV absorption spectra of the solutions prepared at different concentrations (2–24 μg/ml) in its binary mixture with IB were recorded against methanol and smoothed at $\Delta\lambda = 2$ nm, then divided by the smoothed $\Delta\lambda = 2$ nm spectrum of standard solution of IB (14 μg/ml in methanol), the ratio spectra were obtained. The second derivative was calculated for the obtained spectra with $\Delta\lambda = 8$ nm. The amplitudes at 238.9 nm were measured and found to be proportional to the concentration of PA.

### 2.5. Sample preparation

Twenty tablets were weighed and finely powdered in a mortar, an amount of the tablets powder equivalent to 100 mg IB and 162.5 mg PA was dissolved in about 60 ml methanol and filtered in a 100 ml measuring flask, the residue was washed three times with 10 ml methanol, then completed to the mark with the same solvent, appropriate solutions were prepared by taking suitable aliquots of this solution.

## 3. Results and discussion

The UV zero spectra of IB (6 μg/ml), PA (10 μg/ml) in methanol and their mixture are produced in Fig. 1. It is clear that the spectra of the two drugs display considerable overlap, hence the direct UV absorption spectra seems to be difficult for their individual determination in a binary mixture.

### 3.1. Derivative ratio spectra method

The advantages of the derivative ratio spectra method over the zero-crossing derivative method, is the possibility of performing

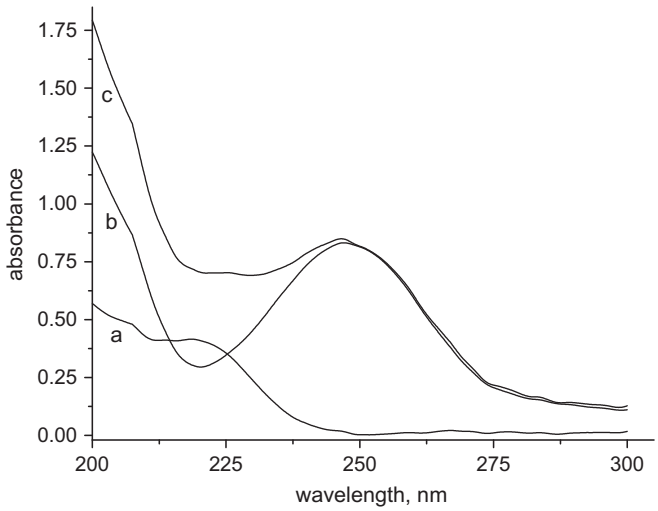



**Figure 1** Zero order spectra of (a) 6 μg/ml IB, (b) 10 μg/ml PA and (c) their mixture.

measurements in correspondence of peaks, hence, a potentially greater sensitivity and accuracy, also in the derivative ratio method the easy measurement on the separate peaks and no need to work only at zero-crossing point as in case of derivative methods. To optimize the simultaneous determination of IB and PA by using $^{1}$DD in case of IB and $^{2}$DD in case of PA, it is necessary to test the influence of the variable: divisor standard concentration, $\Delta\lambda$, and smoothing functions. All of these variables were studied. For the determination of IB, the smoothed at $\Delta\lambda = 2$ nm UV spectra of IB standard solutions of increasing concentrations in methanol in its binary mixture with PA were divided by the spectrum of various divisor concentrations smoothed at $\Delta\lambda = 2$ nm, and the first derivative of the spectrum obtained were calculated, the results show that a standard spectrum of 20 μg/ml of PA was considered as suitable divisor for the determination of IB, also the influence of $\Delta\lambda$ for obtaining the first derivative of the ratio spectra was tested and $\Delta\lambda = 4$ nm was selected as optimum value. The spectra are represented in Fig. 2. The concentration of IB was proportional to the amplitude at 225.6 nm in the concentration range 2–32 μg/ml. Similarly for determination of PA, the smoothed at $\Delta\lambda = 2$ nm UV spectra of PA standards of increasing concentrations in methanol in its binary mixture with IB were divided by the spectrum of various divisor concentrations smoothed at $\Delta\lambda = 2$ nm and the second derivative of the spectrum obtained were calculated. The results show that a standard spectrum of 14 μg/ml of IB was considered as a suitable divisor for the determination of PA, and the optimum value of $\Delta\lambda$ was found equals 8 nm, the obtained spectra are represented in Fig. 3. As seen in the figure there exist two maxima (238.9 and 241.3 nm) and two minima (244.6 and 247.0 nm), we found that measured signals at these wavelengths are proportional to the concentration of the drug in the concentration range 2–24 μg/ml, 238.9 nm was selected for the determination of the synthetic mixtures and commercial tablets due to the low standard deviation and suitable mean recovery. For $^{1}$DD and $^{2}$DD methods, the characteristic parameter of regression equations, and detection limit (Miller and Miller, 1993) are given in Table 1. The regression curve was calculated by the least squares method. The correlation coefficients were near unity indicating good linearity.

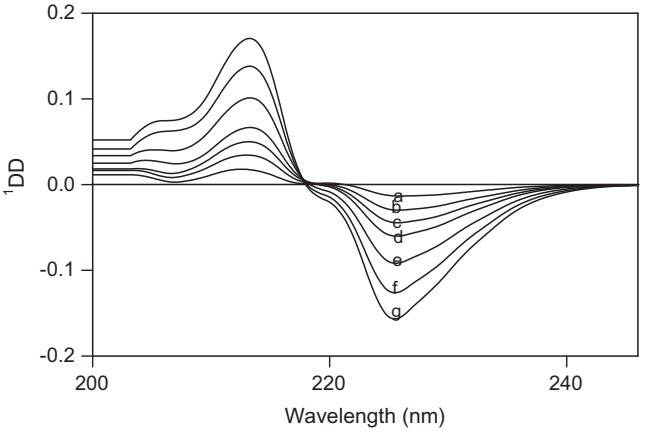



**Figure 2** First derivative of the ratio method of a, 2; b, 4; c, 6; d, 8; e, 12; f, 16; g, 20 μg/ml solution of ibuprofen when 20 μg/ml solution of paracetamol used as divisor.

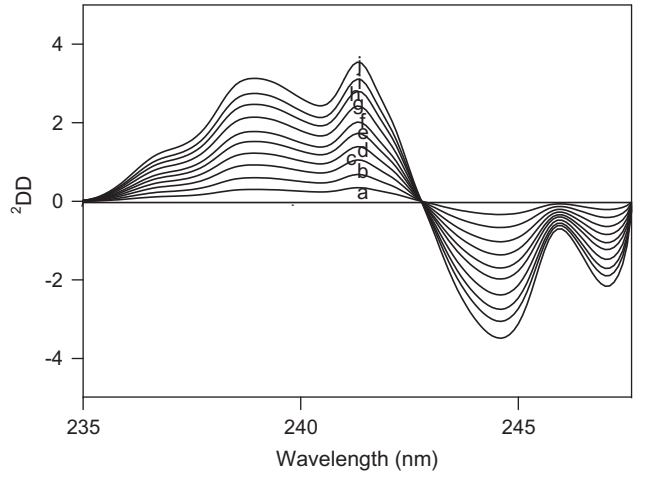



**Figure 3** Second derivative of the ratio method of a, 2; b, 4; c, 6; d, 8; e, 10; f, 12; g, 14; h, 16, i, 18; j, 20 μg/ml solution of paracetamol when 14 μg/ml solution of ibuprofen used as divisor.

**Table 1** Statistical analysis of calibration graphs in the determination of IB and PA using derivative ratio method.

| Parameter | $^1$DD IB | $^2$DD PA |
|---|---|---|
| $\lambda_{max}$ (nm) | 225.6 | 238.9 |
| Linearity (μg/ml) | 2–32 | 2–24 |
| Detection limit (μg/ml) (Miller and Miller, 1993) | 0.53 | 0.57 |
| *Regression equation (Y)*[a] | | |
| Slope ($b$) | $-8.15\times10^{-3}$ | 0.15539 |
| SD of slope ($S_b$) | $4.76\times10^{-5}$ | 0.00134 |
| Intercept ($b$) | $4.25\times10^{-3}$ | −0.02537 |
| SD of intercept ($S_a$) | $8.28\times10^{-4}$ | 0.01864 |
| Correlation coefficient | 0.9999 | 0.9997 |
| SD | $1.43\times10^{-3}$ | $2.96\times10^{-2}$ |

[a] $Y = a + bC$ where $C$ is the concentration in μg/ml and $Y$ is the amplitude at the specified wavelength.

In order to demonstrate the validity and applicability of the proposed methods, recovery studied were performed by analyzing synthetic mixtures of IB and PA which represent different composition ratios, the results are summarized in Table 2. Satisfactory recoveries with small standard deviations were obtained which indicated the high repeatability and accuracy of the two proposed methods.

### 3.2. Analysis of tablets

The proposed method was applied to the determination of IB and PA in commercial Cetofen tablets (200 mg IB and 325 mg PA per tablet). Satisfactory results were obtained for both drugs and were in a good agreement with the label claims and indicate that there is no interference from the excipients used in the formulation of the tablets (Table 3).

**Table 2** Results obtained for laboratory prepared synthetic mixtures using the proposed derivative ratio method.

| Sample | Taken (μg/ml) | | Recovery (%) | |
|---|---|---|---|---|
| | IB | PA | $^1$DD IB | $^2$DD PA |
| 1 | 6 | 6 | 97.65 | 98.08 |
| 2 | 6 | 8 | 99.49 | 101.31 |
| 3 | 6 | 10 | 98.26 | 98.77 |
| 4 | 6 | 14 | 97.85 | 99.25 |
| 5 | 8 | 6 | 100.54 | 101.15 |
| 6 | 10 | 6 | 102.64 | 100.79 |
| 7 | 12 | 6 | 101.07 | 102.23 |
| 8 | 14 | 6 | 101.88 | 103.47 |
| 9 | 16 | 6 | 98.04 | 101.61 |
| 10 | 10 | 8 | 103.87 | 102.21 |
| 11 | 10 | 12 | 102.88 | 100.17 |
| 12 | 10 | 14 | 102.27 | 100.09 |
| 13 | 10 | 20 | 99.20 | 100.96 |
| 14 | 10 | 22 | 99.45 | 99.95 |
| 15 | 14 | 10 | 102.50 | 101.79 |
| 16 | 16 | 10 | 101.04 | 102.30 |
| 17 | 20 | 10 | 102.06 | 103.42 |
| Mean recovery (%) | | | 100.39 | 100.84 |
| SD (%) | | | 2.006 | 1.533 |
| RSD (%) | | | 1.998 | 1.520 |

**Table 3** Recovery results for IB and PA in commercial Cetofen tablets using derivative of the ratio method.

| Taken (μg/ml) | | $^1$DD (IB) | | $^2$DD (PA) | |
|---|---|---|---|---|---|
| IB | PA | Recovery (%) | RSD | Recovery (%) | RSD |
| 6.0 | 9.75 | 96.88 | 0.698 | 97.32 | 0.603 |
| 10.0 | 16.25 | 97.61 | 0.513 | 98.17 | 0.337 |
| 14.0 | 22.75 | 96.01 | 0.899 | 97.29 | 0.621 |

**Table 4** Statistical comparison between results of commercial tablets Cetofen applying derivative of the ratio method.

| Parameter | $^1$DD | $^2$DD | Reference method (Basu et al., 1998) | |
|---|---|---|---|---|
| | IB | PA | IB | PA |
| Mean recovery (%) | 96.83 | 97.59 | 97.16 | 96.62 |
| SD | 0.680 | 0.507 | 1.212 | 0.630 |
| RSD | 0.702 | 0.520 | 1.247 | 0.652 |
| $F$-ratio (9.28)[a] | 3.177 | 1.544 | | |
| $t$-Test (2.447)[b] | 0.475 | 2.398 | | |

Average of four determinations.
SD: Standard deviation.
RSD: Relative standard deviation.
[a] Tabulated $F$-value at 95% confidence level.
[b] Tabulated $t$-value at 95% confidence level and six degrees of freedom.

The results obtained by using the proposed method were statistically compared with the reported least squares method (Basu et al., 1998) using student $t$- and $F$-test (at 95% confidence level) (Miller and Miller, 1993). The results (Table 4) show that the calculated $t$- and $F$-values were less than the theoretical ones, indicating no significant difference between the proposed and reported methods.

## 4. Conclusions

The proposed method is simple, rapid and permit direct determination of ibuprofen and paracetamol in binary mixtures and in tablets without previous separations with good accuracy and precision. Moreover, it has many advantages over separation techniques such as HPLC methods that need more sophisticated instruments which are not available in many laboratories. The methods reported for the determination of IB and PA in mixture are very limited, only spectrophotometry, titrimetric and HPLC methods described. The new reported method is used for the determination of the two pharmaceutical compounds IB and PA in their pharmaceutical preparations where several excipients are present.

## References

Abdel-Hay, M.H., Korany, M.A., Bedair, M.M., Gazy, A.A., 1990. Anal. Lett. 23, 281.
Adams, S.S., Bresloff, P., Mason, C.G., 1976. J. Pharm. Pharmacol. 28, 256.

Affalion, H., Keim, N., Strerescue, M., 1982. Rev. Chim. 11, 14.
Babu, M.N., 1998. Indian Drugs 35, 32.
Basu, D., Mahalanabis, K.K., Roy, B., 1998. J. Pharm. Biomed. Anal. 16, 809.
Blazheevsskii, M.E., Bondarenko, N.U., 2004. Farmatsevtichnii Zhumal (Kiev) 5, 68.
Canaparo, R., Mumtoni, E., Zara, G.P., Dellapena, C., Berno, E., Costa, M., Endi, M., 2000. Biomed. Chromatogr. 14, 219.
Cline Love, L.J., Zibas, S., Noroski, J., Arunyanart, M., 1985. J. Pharm. Biomed. Anal. 3, 511.
Filho, O.F., Lupetti, K.O., Vieira, I.C., 2001. Talanta 55, 685.
Gayal, R.N., Singh, S.P., 2006. Electrochim. Acta 51, 3008.
Hamm, M.J., 2000. Crit. Care Nurse 20, 69.
Hercegova, A., Sadecka, J., Polansky, J., 2000. Electrophersis 21, 2842.
Hergert, L.A., Escandar, G.M., 2003. Talanta 60, 235.
Hussain, S., Murty, A.S.R., Narasimha, R., 1989. Indian Drugs 26, 557.
Ivaska, A., Ryan, T., 1981. Collect. Czech. Chem. Commun. 46, 2865.
Jiong, Z., Huimin, S., Zhihua, Y., Songjiu, T., 2004. Yaowu Fenxi Zazhi 24, 417.
Knochen, M., Giglio, J., Ries, B.F., 2003. J. Pharm. Biomed. Anal. 33, 191.
Liu, X., Liu, L., Chen, H., Chen, X., 2007. J. Pharm. Biomed. Anal. 43, 1700.
Manzoori, J.L., Amjadi, M., 2003. Spectrochim. Acta A 59, 909.
Meyer, J., Karst, U., 2001. Chromatographia 54, 163.
Miller, J.C., Miller, J.N., 1993. Statistics for Analytical Chemistry, third ed. Ellis Horwood, Chichester.
Oliva, M.A., Olsina, R.A., Masi, A.N., 2005. Talanta 66, 229.
Parimoo, P., Sethuraman, R.R., Amalraj, A., Seshadri, N., 1989. Indian Drugs 26, 704.
Persson-Stubberud, K., Astrom, O., 1999. J. Chromatogr. A 798, 307.
Ravisankar, S., Vasudevan, M., Gandhimmathi, M., Suresh, B., 1998. Talanta 46, 1577.
Sharaf El-Din, M.K., Abuirjeie, M.A., Abdel-Hay, M.H., 1991. Anal. Lett. 24.
Teng, X.W., Wang, S.W.J., Davies, N.M., 2003. J. Chromatogr. B 796, 225.
Vermeulen, B., Remon, J.P., 2000. J. Chromatogr. B: Biomed. Sci. Appl. 749, 243.
Way, B.A., Wilhite, T.R., Smith, C.H., Landt, M.J., 1997. Clin. Lab. Anal. 11, 336.