Simultaneous determination of pamabrom and paracetamol in bulk powders and womankit® tablets using spectrophotometric and chemometric-assisted spectrophotometric methods

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ABSTRACT

Five methods were developed for simultaneous determination of pamabrom and paracetamol without previous separation. In the first and second methods pamabrom and paracetamol were determined using second and third derivative UV spectrophotometry with zero crossing measurement at 301 and 265 nm for second derivative method and at 290 and 257 nm for third derivative method, for pamabrom and paracetamol, respectively. The third method depends on first derivative of the ratios spectra by measurements of the amplitudes at 271 nm for pamabrom and at 258 nm for paracetamol. The fourth one depends on two wavelength measurement for the total content of the two drugs at 222 and 265 nm, while the content of paracetamol was determined by measuring the absolute value of the first derivative curve at 243 nm. The fifth method describes the use of multivariate spectrophotometric calibration for the simultaneous determination of the analyzed binary mixture where the resolution is accomplished by using classical least squares regression analysis. All the proposed methods were extensively validated and the results obtained were statistically analyzed and compared with those obtained by official methods. The results obtained were statistically analyzed and proved to be precise and accurate.

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KEYWORDS

Pamabrom; Paracetamol; Second derivative spectrophotometry; Third derivative spectrophotometry; Ratio derivative spectrophotometry; Two wavelength method; Multivariate; Pharmaceutical dosage form.

INTRODUCTION

Pamabrom (PAM) Paracetamol (PAR)
Pamabrom (PAM) Paracetamol (PAR) Paracetamol (PAR), chemically 4′-hydroxy acetanilide, is a centrally and peripherally acting non-opioid analgesic and antipyretic[1]. The USP describes a titrimetric method for the determination of PAR[2]. Literature survey reveals, the presence of spectrophotometric[3-7], Electrochemical[8-10], HPLC[11-15] and HPTLC[16-18] methods reported for the estimation of PAR in pharmaceutical formulations.

Pamabrom (PAM), (8-Bromo-3,7-dihydro-1,3-dimethyl-1-H-purine-2,6-dione with 2-amino-2-methyl-1-propanol)[2], its structure is similar to caffeine and theobromine and like these compounds it is a diuretic, mild stimulant, and bronchodilator. Hitherto, no method except the USP one[2] was introduced for the determination of pamabrom as a single component. However, two methods have been reported for determination of the two constituents in compound PAR and PAM tablets in human plasma by high performance liquid chromatography[19, 20].

Derivative spectrophotometry has been found to be a useful method in the determination of mixtures with two or more components having overlapping spectra and in eliminating interference from formulation matrix by using the zero-crossing techniques[21-23].

Ratio-spectra derivative spectrophotometric method has also been found to be useful in the estimation of drugs in their mixtures. This method permits the determination of a component in their mixture at the wavelengths corresponding to a maximum or minimum and also the use of peak-to-peak between consecutive maximum and minimum. The main advantage of derivative of the ratio-spectra method may be the chance of easy measurements in correspondence of peaks so it permits the use of the wavelength of highest value of analytical signals (maximum or minimum). Moreover, the presence of a lot of maxima and minima is another advantage by the fact that these wavelengths give an opportunity for the determination of active compounds in the presence of other active compounds and excipients which possibly interferes the analysis[24-26].

The two wavelength technique was extended for the analysis of two drugs in their binary formulation. Where, the spectra of two drugs are crossed at certain points, these points are so-called “isosbestic points” at which the two drugs have the same absorptivity, so the mixture of the two drugs act as single component that condemns the absorbance at isosbestic points as good measurements of the total concentration of both drugs in combination, if the concentration of either two drugs could be determined, separately, the concentration of the second one could be calculated by subtraction[27, 28].

The classical least squares (CLS) method of analysis is one of the simplest multivariate methods that can be performed with readily acceptable statistical software. By using multivariate calibration methods, it is possible to obtain a model adjusted to the concentration values of the mixtures used in the calibration stage and then use this model to estimate the analyte concentration in samples such as drugs in pharmaceutical preparations[24, 29, 30].

The aim of this paper was to demonstrate the capability of second and third derivative spectrophotometry, derivative ratio spectrophotometry, two wavelength method and classical least squares for simultaneous analysis of PAM and PAR in mixture form without the need of preliminary separation steps. In which, to the best of our knowledge no method is available in the literature for the simultaneous determination of both drugs in their dosage form.

**EXPERIMENTAL**

**Apparatus**

UV-Visible Spectrophotometer, Shimadzu UV-1800 is connected to an IBM compatible computer. The software was UVPC personal spectroscopy software version 3.7 (Shimadzu). The absorption spectra of the reference and test solutions were carried out in a 1 cm quartz cells. The data was then exported into MICROSOFT EXCEL program. The chemometric calculations were done with MATLAB 5.3 program.

**Chemicals and reagents**

All the chemicals used were of Analytical Reagent grade and the solvents were of spectroscopic grade.

Pure samples: Pure pamabrom and paracetamol were kindly supplied by international drug agency for pharmaceutical industry (Portsaid, Egypt). Their percentage purities were certified and analyzed by official USP methods[2] and were found to be for pamabrom
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99.88 ± 0.78 (expressed as 8-bromotheophylline) and 99.74 ± 0.79 for paracetamol. They were used as provided.

Market samples: Womankit® tablets; each tablet is claimed to contain 500 mg PAR and 20 mg PAM, B.N. 11190 (manufactured by IDI, Portsaid, Egypt for Haya Pharm) was purchased from Egyptian market.

Methanol: was obtained from Merck (Darmstadt, Germany).

Standard stock and working solutions

- PAM standard stock solution; 0.5 mg/mL in methanol.
- PAR standard stock solution; 0.5 mg/mL in methanol.
- PAM standard working solution; 0.1 mg/mL in methanol.
- PAR standard working solution; 0.1 mg/mL in methanol.

Procedures

Spectral characteristics of PAM and PAR

The zero-order (D₀) absorption spectra of 1-50 µg/mL of PAM and 5-50 µg/mL of PAR solution were recorded against methanol as a blank over the range of 200–400 nm.

Construction of calibration curves

Aliquots equivalent to 10-500 µg of PAM and 50-500 µg of PAR were accurately transferred from their standard working solutions into two separate series of 10-mL volumetric flasks then completed to volume with methanol. The spectra of the prepared standard solutions are scanned from 200-400 nm and stored in the computer.

Second derivative spectrophotometric method

The values of the D₂ amplitudes were measured at 301 nm (zero-crossing of PAR) and 265 nm (zero-crossing of PAM) for the determination of PAM and PAR, respectively. The D₂ amplitudes were then plotted against the final concentrations to get the calibration graphs and the corresponding regression equations were derived.

First derivative of the ratio spectrophotometric method

For the determination of PAM the stored spectra of PAM were divided by the spectrum of 40 µg/mL PAR then the first derivative of the ratio spectra (D₁) with Δλ = 4 nm is obtained. The amplitude of the first derivative peak of (PAM/PAR) is measured at 271 nm. A calibration graph relating the peak amplitude at 271 nm to the corresponding concentrations in µg/mL of PAM is constructed.

Alternatively, for the determination of PAR the stored spectra of PAR were divided by the spectrum of 40 µg/mL PAM then the first derivative of the ratio spectra (D₁) with Δλ = 4 nm is obtained. The amplitude of the first derivative peak of (PAR/PAM) is measured at 258 nm. A calibration graph relating the peak amplitude at 258 nm to the corresponding concentrations in µg/mL of PAR is constructed.

Two wavelength method (2WS)

In 10-mL volumetric flasks, aliquots of PAM and PAR were accurately transferred from their corresponding stock solutions, to prepare mixtures containing different ratios of each of the two drugs in their binary mixtures. For analysis of PAM/PAR binary mixture, the absorbance of the resulting solutions were measured at 222 nm and 265 nm corresponding to the total content of PAM and PAR in their binary mixture and the values of the D₁ amplitudes were measured at 243 nm (zero-crossing of PAM) corresponding to the content of PAR. The concentration of PAR was subtracted from the total concentrations of PAM and PAR to get the concentration of PAM. Construct a calibration curve relating the absorbance of the zero order spectra of PAM at wavelengths 222 nm and 265 nm to the corresponding concentrations in µg/ml of PAM. Construct a calibration curve relating the absorbance of the first derivative spectra of PAR at λ = 243 nm to the corresponding concentrations in µg/ml of PAR.

Classical least squares method

Two training sets for CLS were constructed by di-
(sol)uting different volumes of PAM and PAR working solutions into 10-mL volumetric flasks and completing to volume with methanol to reach the studied concentrations. The first training set (A1) contains pure samples of PAM and PAR separately, while the second training set (A2) was constructed with different mixtures of PAM and PAR. The zero order absorbance spectra were measured and stored in the computer. To estimate the CLS models for both training set A1 and A2, the computer was fed with the absorbance and concentration matrices, then calculations were carried out and two models M1 and M2 were obtained for both training sets A1 and A2, respectively.

**Determination of PAM and PAR in laboratory prepared mixtures**

Accurately measured aliquots of the working standard solutions of both drugs were transferred into a series of 10-mL volumetric flasks to prepare several synthetic mixtures with different ratios. The solutions were then diluted with methanol to volume and mixed well. These prepared mixtures were then analyzed as described under construction of the calibration graphs.

**Determination of PAM and PAR in Pharmaceutical preparation**

For all methods, five tablets were pulverized well; an accurate amount of the powdered tablets equivalent to 10 mg PAM and 250 mg PAR was weighed and transferred into a 100-mL volumetric flask. The volume was completed with methanol. The resulting solution was sonicated for 10 min and filtered then the procedure described under construction of the calibration graphs was carried out.

**RESULTS AND DISCUSSION**

PAM is co-formulated with PAR in Womankit® tablets, where the concentration of PAR is 25 times that of PAM. The aim of this work is to develop simple and accurate methods for the determination of both drugs in presence of each other. Molecular absorption spectroscopy has been widely used for the analysis of drugs in pharmaceutical preparations with a view to the development of analytical methods. The use of this technique for pharmaceutical analysis has the inherent constraint that most active drugs absorb in the UV region and exhibit strongly overlapped spectra that impede their simultaneous determination. From analyzing the zero order absorption spectra of both drugs, it was obvious that the spectra PAR completely masks that of PAM when their ratio is 25 : 1 (PAR : PAM) which inhibits the analysis of PAM as a minor ingredient in the dosage form. On the other hand, the zero order absorption spectra (D₀) of higher concentrations of PAM showed that PAM exhibits absorbance at 248 nm which is the λ_max of PAR (Figure 1), thus, in higher concentrations the spectra of both drugs will show a certain degree of overlap hindering the determination of either drug in presence of the other.

**Second derivative spectrophotometric method**

Figure 2 shows the second derivative spectra of
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The third derivative spectra of PAM (Figure 3) showed the applicability of its determination by measurement of its $D^3$ amplitude at the zero-crossing of PAR at 290 nm. Also, PAR was determined by measuring its $D^3$ amplitude at 257 nm; the zero crossing wavelength of PAM (Figure 3). The calibration graphs were rectilinear in the concentration ranges 1-50 µg/mL and 5-50 µg/mL for PAM and PAR, respectively.

**First derivative of the ratio spectrophotometric method**

The main parameters that affect the shape of the ratio spectra which are wavelength, the concentration of the standard solution used as a divisor and the wavelength increment over which the derivative is obtained ($\Delta\lambda$) were carefully tested. The ratio spectra presented in Figure 4, 5 and the first derivative of the ratio spectra presented in Figure 6, 7 may provide a good proof for this understanding. Regarding the effect of divisor concentration, different concentrations of divisor (15, 40, 50 µg/mL) for PAM and (15, 30, 40 µg/mL) for PAR were used. The divisor concentrations 40 µg/mL for both drugs were found the best regarding average recovery percent when they were used for the prediction of PAM and PAR concentrations in bulk powder and in laboratory prepared mixtures. The choice of wavelength for the measurement was carefully studied. For the determination of PAM, measuring at 223 and 271 nm was carried out, good linearity was observed but the recovery percent at 271 nm was the best, which might be attributed to its higher signal to noise ratio. On the other hand, for determination of PAR, measuring at 233 and 258 nm was...
In the two wavelength method, total concentration of both drugs in the mixture (T) was determined at the previously chosen wavelengths. This theory could be confirmed experimentally by recording the absorbance spectra of 20 µg/mL of PAM and PAR, each separately and in a mixture containing same total concentration (10 µg/mL of each) as shown in Figure 8. The concentration of PAR (B) was determined by measurement of its first derivative amplitude at 243 nm (λ₁); the zero-crossing of PAM, which showed a linear correlation in the concentration range 5-50 µg/mL (Figure 9). The concentration of PAM could be calculated by subtracting B out of T and the linearity between the zero order absorption spectra of PAM at 222 nm (λ₁) and 265 nm (λ₂) and the corresponding concentrations of the drug was studied and it showed good linearity in the concentration range of

Figure 5: Ratio spectra of PAR (5-50 µg/mL), divisor is 40 µg/mL PAM.

Figure 6: First derivative of ratio spectra of PAM (1-50 µg/mL) at 271 nm, using 40 µg/mL PAR as divisor.

Figure 7: First derivative of ratio spectra of PAR (5–50 µg/mL) at 258 nm, using 40 µg/mL PAM as divisor.
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1-50 µg/mL and for PAM.

**Classical least squares method**

Chemometrics is a technique that is gaining wide application for the resolution of drug mixtures. Therefore, CLS was applied for the simultaneous determination of PAM and PAR. To produce a calibration using the CLS, we started with a training set consisting of a concentration matrix, C, and an absorbance matrix R, for known calibration samples (the calibration samples can either be the pure components separately (training set A₁) or mixture of known concentrations of the constituents (A₂)). Both PAM and PAR in the validation samples are reasonably distributed and span a wide range of concentration for both drugs.

**VALIDATION OF THE METHODS**

**Linearity**

The linearity of the methods was evaluated by analyzing 10 concentrations of PAM and 9 concentrations of PAR ranging between 1-50 µg/mL and 5–50 µg/mL, respectively. Each concentration was repeated three times; in order to provide information on the variation of spectrophotometric values between samples of same concentration. The assay was performed according to the experimental conditions previously mentioned. The different calibration graphs were found to be rectilinear over the concentration ranges cited in TABLE 1. The validity of the proposed method was evaluated by statistical analysis of the regression data regarding the standard deviation of the residuals (S_y/x), standard error of the intercept and the standard error of the slope, where the small values of the figures indicate the high accuracy and precision of the method.

**Accuracy and precision**

The accuracy of the results was checked by applying the proposed methods for determination of different blind samples of PAM and PAR. The concentrations were obtained from the corresponding regression equations. From which the percentage recoveries were calculated, then compared with those of official methods [2]. Statistical analysis [31] of the results obtained by the proposed and official methods using Student’s t-test and variance ratio F-test showed no significant dif-

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Figure 8: Absorption spectra of 20 µg/mL PAR (---), 20 µg/mL PAM (——) and a binary mixture of 10 µg/mL PAM and 10 µg/mL PAR (+++).

Figure 9: First derivative zero crossing determination of 20 µg/mL PAR (—) at 243 nm against 20 µg/mL PAM (......).
ferences between them regarding accuracy and precision, respectively (TABLE 2 & 3).

Intraday (repeatability) and interday (intermediate) precisions were assessed using three concentrations and three replicates of each concentration. The relative standard deviations were found to be very small indicating reasonable repeatability and intermediate precision of the proposed methods (TABLE 4).

**Specificity**

The specificity of each of the proposed methods was investigated by observing any interference encountered from common dosage form excipients. It was shown that these compounds did not interfere with the results of the proposed methods.

**Limit of Detection (LOD) and Limit of Quantification (LOQ)**

The LOD is the lowest concentration of the drug that can be detected, but not necessarily quantitated, under the stated experimental conditions, while, the LOQ is the lowest concentration of the analyte that...
TABLE 4: Intraday and interday statistical data for the determination of PAM and PAR by the proposed methods.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D1 (λs)</th>
<th>D2</th>
<th>D3</th>
<th>1DD</th>
<th>CLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraday</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>99.29 ± 0.79</td>
<td>99.57 ± 0.90</td>
<td>100.09 ± 0.67</td>
<td>99.55 ± 0.80</td>
<td>99.92 ± 0.71</td>
</tr>
<tr>
<td>% RSD</td>
<td>0.79</td>
<td>0.90</td>
<td>0.67</td>
<td>0.80</td>
<td>0.71</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Variance</td>
<td>0.63</td>
<td>0.81</td>
<td>0.44</td>
<td>0.64</td>
<td>0.51</td>
</tr>
</tbody>
</table>

* Average of three different determinations.
Values in parenthesis are the corresponding theoretical values of t and F at (p = 0.05).

**Inter-day**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D1 (λs)</th>
<th>D2</th>
<th>D3</th>
<th>1DD</th>
<th>CLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>99.74 ± 0.79</td>
<td>99.57 ± 0.90</td>
<td>100.09 ± 0.67</td>
<td>99.55 ± 0.80</td>
<td>99.92 ± 0.71</td>
</tr>
<tr>
<td>% RSD</td>
<td>0.79</td>
<td>0.90</td>
<td>0.67</td>
<td>0.80</td>
<td>0.71</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Variance</td>
<td>0.63</td>
<td>0.81</td>
<td>0.44</td>
<td>0.64</td>
<td>0.51</td>
</tr>
</tbody>
</table>

The intraday (n = 3), average of three concentrations for PAM and PAR repeated three times within the day.
The interday (n = 3), average of three concentrations for PAM and PAR repeated three times in three successive day.
can be determined with acceptable precision and accuracy. Both LOD and LOQ were calculated according to ICH recommendations\(^3\) and the results are abridged in TABLE 1.

**Stability**

The working solutions of the studied drugs exhibited no spectrophotometric changes for more than one week when stored at 4°C.

**APPLICATIONS**

**Analysis of laboratory prepared mixtures**

The proposed methods were successfully applied to the analysis of PAM and PAR in laboratory prepared mixtures containing both drugs in different ratios. The average percent recoveries were based on the average of three replicate determinations (TABLE 5).

**Analysis of Dosage Forms**

**TABLE 5 : Determination of PAM and PAR in laboratory prepared mixtures by the proposed methods.**

<table>
<thead>
<tr>
<th>Concentration µg/mL</th>
<th>(D_2)</th>
<th>(D_3)</th>
<th>1DD</th>
<th>(2\lambda_s)</th>
<th>(D_1(\lambda_3))</th>
<th>CLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Recovery*</td>
<td>% Recovery*</td>
<td>% Recovery*</td>
<td>% Recovery*</td>
<td>% Recovery*</td>
<td>% Recovery*</td>
</tr>
<tr>
<td>PAM 20.00</td>
<td>99.95</td>
<td>102.34</td>
<td>99.75</td>
<td>100.28</td>
<td>100.25</td>
<td>99.59</td>
</tr>
<tr>
<td>PAR 20.00</td>
<td>100.06</td>
<td>101.45</td>
<td>101.34</td>
<td>99.87</td>
<td>100.56</td>
<td>100.67</td>
</tr>
<tr>
<td>PAM 10.00</td>
<td>99.95</td>
<td>100.76</td>
<td>99.01</td>
<td>100.96</td>
<td>99.75</td>
<td>100.56</td>
</tr>
<tr>
<td>PAR 20.00</td>
<td>25.00</td>
<td>99.55</td>
<td>99.75</td>
<td>100.00</td>
<td>100.25</td>
<td>100.50</td>
</tr>
<tr>
<td>PAM 2.00</td>
<td>50.00</td>
<td>100.09</td>
<td>100.86</td>
<td>100.25</td>
<td>101.87</td>
<td>99.09</td>
</tr>
<tr>
<td>PAR 5.00</td>
<td>50.00</td>
<td>100.50</td>
<td>100.59</td>
<td>100.05</td>
<td>100.00</td>
<td>100.75</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>100.02</td>
<td>100.96</td>
<td>100.07</td>
<td>100.54</td>
<td>100.15</td>
<td>100.51</td>
</tr>
<tr>
<td>% RSD</td>
<td>± 0.31</td>
<td>± 0.87</td>
<td>± 0.76</td>
<td>± 0.75</td>
<td>± 0.62</td>
<td>± 0.87</td>
</tr>
<tr>
<td>% Rer</td>
<td>0.12</td>
<td>0.35</td>
<td>0.31</td>
<td>0.31</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>Variance</td>
<td>0.09</td>
<td>0.76</td>
<td>0.58</td>
<td>0.57</td>
<td>0.39</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Average of three different determinations.

**TABLE 6 : Statistical analysis of the results obtained by the proposed methods and official methods\(^2\) for the analysis of PAM and PAR in Womankit® tablets.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(D_2)</th>
<th>(D_3)</th>
<th>1DD</th>
<th>(2\lambda_s)</th>
<th>(D_1(\lambda_3))</th>
<th>CLS</th>
<th>Official methods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAM</td>
<td>PAR</td>
<td>PAM</td>
<td>PAR</td>
<td>PAM</td>
<td>PAR</td>
<td>PAM</td>
</tr>
<tr>
<td>Mean* ± SD</td>
<td>99.83 ± 0.67</td>
<td>101.13 ± 0.95</td>
<td>99.62 ± 0.72</td>
<td>100.88 ± 0.94</td>
<td>99.06 ± 0.81</td>
<td>100.51 ± 0.70</td>
<td>99.19 ± 0.89</td>
</tr>
<tr>
<td>SD</td>
<td>0.73</td>
<td>0.81</td>
<td>0.70</td>
<td>0.79</td>
<td>0.81</td>
<td>0.70</td>
<td>0.90</td>
</tr>
<tr>
<td>% RSD</td>
<td>0.67</td>
<td>0.94</td>
<td>0.73</td>
<td>0.93</td>
<td>0.81</td>
<td>0.70</td>
<td>0.37</td>
</tr>
<tr>
<td>% Rer</td>
<td>0.27</td>
<td>0.39</td>
<td>0.30</td>
<td>0.38</td>
<td>0.33</td>
<td>0.28</td>
<td>0.37</td>
</tr>
<tr>
<td>Variance</td>
<td>0.45</td>
<td>0.91</td>
<td>0.52</td>
<td>0.88</td>
<td>0.65</td>
<td>0.49</td>
<td>0.30</td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>t- test</td>
<td>1.812</td>
<td>0.877</td>
<td>1.292</td>
<td>0.481</td>
<td>0.101</td>
<td>0.171</td>
<td>0.342</td>
</tr>
<tr>
<td>F- test</td>
<td>1.297</td>
<td>1.139</td>
<td>1.118</td>
<td>1.096</td>
<td>1.109</td>
<td>1.630</td>
<td>1.360</td>
</tr>
</tbody>
</table>

*Mean of recovery for PAM and PAR in three different determinations in Womankit® tablets.

The proposed \(D_1\), \(D_2\), \(D_3\), 1DD, two wavelength, and CLS methods were applied for the simultaneous determination of PAM (as 8-bromotheophylline) and PAR in Womankit® tablets. The performance of the proposed methods were statistically compared with that of the official methods\(^2\) by Student’s t-test and F-val-
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CONCLUSION

For routine analytical purposes, it is always of interest to establish methods capable of analyzing a large number of samples in a short time period with due accuracy and precision. Spectrophotometric techniques can generate large amounts of data within a short period of analysis; however, when coupled with chemometrics tools, the quality of the spectral information can be markedly increased, converting this combined technique into a powerful and highly convenient analytical tool. In this paper, a study of the use of spectrophotometric methods for the resolution of PAM and PAR in their multicomponent mixtures have been accomplished, showing that D$_2$, D$_3$, DD, two wavelength and CLS methods provide, with adequate software support, a clear example of the high resolving power and low cost of this technique.

REFERENCES