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Determination of caffeine in pharmaceutical preparations by the Linear Absorbances Method

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In this work a fast Linear Absorbance Method for the determination of caffeine in pharmaceutical preparations in the presence of paracetamol or acetylsalicylic acid is presented. The determination of acetylsalicylic acid or paracetamol is also possible by means of a tabulated parameter f^B, which values are included in this paper. The method avoids the use of separation steps or multicalibration methods. The determination was carried out in commercial preparations with good results.

1. Introduction

Caffeine is a well-known methylxanthine, commonly used as a cardiotonic or analeptic drug. Moreover, due to its stimulating effect, a lot of analgesic formulations and drinks contain caffeine. Since high doses of caffeine can produce irritation, anxiety and sleeplessness, its determination in samples of pharmaceuticals or biological fluids has attracted interest.

For determination of caffeine in serum or urine, gas chromatography [1], HPLC [2] or electrophoretic [3] techniques are commonly used. However, the determination of caffeine in pharmaceuticals can be performed using spectrophotometric [4], fluorimetric [5] or phosphorimetric [6] methods, these procedures generally include a previous extraction step with the aim of avoiding potential interferences.

Acetylsalicylic acid (ASA) and paracetamol (acetaminophen) are drugs usually associated with caffeine in commercial analgesic formulations. Since the caffeine absorption spectrum presents a maximum absorbance at 272 nm, paracetamol at 255 nm and acetylsalicylic acid at 292 nm, different procedures based on UV absorption have been proposed to resolve mixtures of these compounds. The ternary mixture of caffeine paracetamol and acetylsalicylic acid can be solved by means of different mathematical algorithms based in multiwavelength measurements [7–8], whereas the determination of caffeine in binary mixtures caffeine-paracetamol can be carried out using derivative spectroscopy [9] or mathematical methods [10].

In this paper, we propose the use of the Linear Absorbance Method to determinate caffeine in analgesic formulations. By this method the caffeine determination can be performed without the need to dispose of standard solutions of interfering components or a previous separation step. In addition, the determination of paracetamol and acetylsalicylic acid, can also be carried out using the tabulated f^B value given in this work.

The method has been applied to prepared and commercial samples.

In previous works the theoretical basis [11, 12] and some applications [13, 14] of the "Linear Absorbances Method" were published. The method is based on the mathematical function of the straight line that connects two experimental points A_1^S, ε_1^A and A_2^S, ε_2^A (where A_i^S is the absorbance of the sample and ε_i^A the absorptivity of the analyte at λ_i). This function is, evidently, a non-real function since it is only true for 1 and 2 point. However, this non-real function allows the determination of C^A, by the following mathematical function:

$$C^A = \frac{A_1^S - A_2^S}{\varepsilon_1^A - \varepsilon_2^A} - \frac{A_2^S\varepsilon_1^A - A_1^S\varepsilon_2^A}{A_2^t\varepsilon_1^A - A_1^t\varepsilon_2^A}\,\frac{A_1^t - A_2^t}{\varepsilon_1^A - \varepsilon_2^A} \qquad (1)$$

where, A_1^t and A_2^t are the absorbance values of one solution of the interfering component (B), whos concentration, in this solution, needs not needful to be known (called test solution and labelled by the superindex **t**).

The C^B value can be calculated by the equation:

$$C^B = \frac{A_2^S\varepsilon_1^A - A_1^S\varepsilon_2^A}{A_2^t\varepsilon_1^A - A_1^t\varepsilon_2^A}\,\frac{A_1^t - A_2^t}{\varepsilon_1^A - \varepsilon_2^A}\,f^B \qquad (2)$$

being $f^B = (\varepsilon_1^A - \varepsilon_2^A)/(\varepsilon_1^B - \varepsilon_2^B)$.

To obtain the C^B value, the f^B value is needed. Since f^B is a function of ε_i^B, it must be obtained using standard solutions of B or, to avoid this, a f^B value previously tabulated can be used.

The precision in the C^A value obtained will be better if more than two wavelengths are used. For this purpose more than one couple of wavelengths can be used. Besides, if in a wavelength interval $\lambda_1 - \lambda_2$ there is a linear correlation between A_i^S and ε_i^A, the $A_i^S = f(\varepsilon_i^A)$ can be found using several experimental points (corresponding to different wavelengths) into this interval.

2. Investigations, results and discussion

2.1. Determination of caffeine in the presence of paracetamol

On inspection of the spectra of caffeine and paracetamol the 280–294 nm interval, a linear dependence between ε^B and ε^A seems to be present. This assumption was confirmed by a series of three solutions of paracetamol (with 16, 20 and 24 ppm). These absorbances in the 280 to 294 nm interval ($\Delta\lambda = 2$ nm), were plotted against A_i^A.

The f^B value of paracetamol in the 280–294 interval was determined. Series of 15 solutions with three different concentrations of paracetamol were prepared, and their absorbances were measured on five different days. From the absorbances obtained, the f^B value was calculated, $f^B_{280-294} = 2.95 \pm 0.01$

Besides, a wavelength pair of $\lambda_1 = 276$ and $\lambda_2 = 288$ nm has also been selected. In the $\lambda_1 - \lambda_2$ interval there was no linear correlation between ε^B and ε^A. The f^B value is now determined as described, but using only the absorbance values at λ_1 and λ_2. The obtained value was: $f^B_{276-288} = 1.61 \pm 0.01$.

Using these f^B values, several prepared samples were analysed. The determination of caffeine and paracetamol was

carried out in samples containing 20–24 ppm of paracetamol and 2–4 ppm of caffeine and the bigger error obtained in both, interval and couple of wavelengths procedures, were ≤ 0.4 ppm in all cases.

The combination caffeine-paracetamol is usually found in pharmaceuticals, generally with a large amount of paracetamol and small amount of caffeine. A real sample that presents this composition is the commercial product Analgilasa®, with the following composition: caffeine 30 mg, paracetamol 500 mg, codeine phosphate 10 mg and excipient.

As it has been reported, codeine phosphate shows a maximum absorbance at 284 nm in water and leads to a potential interference; however, due to its small amount and absorptivity, its effect can be neglected.

For the analysis of this pharmaceutical we carried out three replications for each tablet and three tablets were analysed by means of the two procedures. Table 1 shows the results obtained for the 280–294 nm interval and Table 2 the results obtained using the couple of wavelengths.

Table 1: Analysis of Analgilasa®

Present (%)		Found (%)	
Caffeine	Paracetamol	Caffeine	Paracetamol
4.75	79.21	4.84 ± 0.08	80.54 ± 0.07
4.76	79.28	4.82 ± 0.03	78.38 ± 0.09
4.73	78.89	4.74 ± 0.06	$80.5_8 \pm 0.1_6$

wavelength interval 280–294 nm, $f^B = 2.95 \pm 0.01$

Table 2: Analysis of Analgilasa®

Present (%)		Found (%)	
Caffeine	Paracetamol	Caffeine	Paracetamol
4.75	79.21	4.45 ± 0.09	$78.9_6 \pm 0.2_3$
4.76	79.28	4.93 ± 0.05	$77.9_8 \pm 0.1_1$
4.73	78.89	5.00 ± 0.05	$76.9_7 \pm 0.1_2$

$\lambda_1 = 276$ nm and $\lambda_2 = 288$ nm, $f^B = 1.61 \pm 0.01$

2.2. Determination of caffeine in the presence of acetylsalicylic acid

Working under similar experimental conditions and experimental steps, the absorbance values of solutions of ASA were obtained in the 264–270 nm interval. The f^B value for this interval was determined and the mean value obtained was: $f^B = 6.28 \pm 0.03$. The wavelength couple chosen for this A-B system was 276 and 288 nm. The f^B value for this wavelength couple was: $f^B_{276-288} = -3.050 \pm 0.001$

Synthetic samples containing variable amounts of ASA and a fixed content of caffeine were analysed by the proposed procedure and errors obtained were, in all cases, smaller than 0.2 ppm.

The real sample selected, to test the analytical procedure, was the commercially product Cafiaspirina®, which has the following composition: caffeine 0.05 g, acetylsalicylic acid 0.5 g and excipient.

Table 3 shows the caffeine contents found by the two procedures.

Table 3: Analysis of Cafiaspirina®

Caffeine		
Present	Found (%) (wavelength interval)	Found (%) ($\lambda_1 - \lambda_2$)
7.22	$7.9_0 \pm 0.1_0$	6.77 ± 0.04
7.26	$7.7_4 \pm 0.1_6$	7.09 ± 0.08
7.16	7.69 ± 0.02	7.17 ± 0.03

interval of wavelengths 264–270 nm, $\lambda_1 = 276$ nm and $\lambda_2 = 288$ nm

2.3. Conclusions

The determination of caffeine, in presence of large amounts of paracetamol or acetylsalicylic acid, by the Linear Absorbance Method is satisfactory. The proposed procedure also allows the determination of the interfering compound using the f^B value proposed, an option which is mainly suitable for routine analysis.

To improve the precision a linear interval of wavelengths can be used or, if there is not a linear interval, different couples of wavelengths may be used.

Another advantage of the proposed procedure is that, if no caffeine standard is available, it is possible to use standard of paracetamol or ASA and plot A_i^S vs ε_i^B, to find ε_0^A with a test solution of caffeine (with unknown concentration), and to obtain the caffeine concentration in the sample since $f^A = 1/f^B$.

3. Experimental

3.1. Reagents and apparatus

Caffeine, paracetamol and acetylsalicylic acid from Merk. HCl, NaOH, and Na_2CO_3 from Probus. All the reagents used were of analytical grade quality. Molecular absorption spectrophotometer, diode array detector, HP 8452A.

3.2. Experimental procedures for commercial samples

A tablet of the pharmaceutical is powdered; a portion is dissolved in distilled water. The suspension of the sample is filtered and, by appropriate dilution, a series of three solutions containing 2–5 ppm of caffeine in HCO_3^-/CO_3^{2-} buffer (pH $\geq$ 10.5) are prepared and their absorbances are measured at the previously cited wavelengths.

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