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Application of least squares method in matrix form: simultaneous determination of ibuprofen and paracetamol in tablets

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Abstract

Least squares method in matrix form which is *K*-matrix representation of Beer's law is presented for simultaneous determination of ibuprofen and paracetamol in tablets without prior separation from each other. The concentration of each component in the mixture was determined spectrophotometrically from absorbances of the mixture measured at 225, 226, 228, 232, 230, 234, and 235 nm. Mixtures of known composition were used as standards to minimise errors due to presence of both compounds in the same solution. Excellent results were obtained by this method. Published by Elsevier Science B.V.

Keywords: Least-squares method; Spectrometry; Ibuprofen; Paracetamol; Computer analysis

1. Introduction

Tablets containing ibuprofen, an anti-inflamatory agent in combination with an analgesic were found to provide therapeutic effects [1]. Paracetamol was shown to possess analgesic and antipyretic actions [2]. Thus tablets containing ibuprofen and paracetamol showed combined analgesic, anti-inflamatory and antipyretic actions. The combination is widely used in India. Each tablet contains ibuprofen − 400 mg and paracetamol 325 mg. Among manufacturers, Raussel India marketed it as COMBIFLAM and Glaxo India under the name of ZUPAR. The local QA requirement is that each tablet should contain a minimum 9058 and maximum 110% of the declared amount on the tablet. Various spectrophotometric [3–5], titrimetric [6] and chromatographic [7,8] methods were reported for determination of ibuprofen and paracetamol individually. Apart from these methods, the British Pharmacopoeia [9] recommended the titrimetric method for ibuprofen tablets and spectrophotometric method for paracetamol tablets. On the other hand, the United States Pharmacopeia [10] described HPLC method for ibuprofen tablets and column chromatography followed by spectrophotometry for paracetamol tablets. Literature

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survey revealed that only two papers reported methods for simultaneous determination of both compounds in the mixture. One of these [11] used tritimetry for determination of both these compounds simultaneously in the combination preparation whereas the other [12] described HPLC method for determination of ibuprofen, paracetamol and diazepam in multi-component tablets. A simple, rapid and reliable method of assay for quality control of ibuprofen-paracetamol tablets simultaneously would be useful. In our efforts to develop an easy, efficient and practical low-cost method for quantitative analysis of binary pharmaceutical formulations, we explored application of least squares method in matrix form [13–15] with considerable success. In continuation of this study, we report herein, simultaneous determination of ibuprofen and paracetamol in tablets using least squares method in matrix form. Mixtures of known composition were used as standards to minimise error due to presence of both components in the solution. The method was found to give accurate and precise results. The choice of analytical wavelengths was derived by ordering wavelengths through F-value for each wavelength followed by t-test for different set of wavelengths.

2. Experimental

2.1. Theory

It is assumed that Beer's law is applicable to the absorption spectrum of the system investigated. For a multicomponent system, the total absorbance at a single wavelength is $A' = \sum_{i=1}^{N} k_i c_i$, where k_i is the proportionality constant for ith component, c_i is its concentration and N is the number of components. A series of such equations for each wavelength in a spectrum can be written in matrix notation: $A = KC$. When mixtures of known composition are used as standards to minimize errors arising from the presence of both compounds, there is set of absorbances (A) and a set of concentrations (C) for each mixture. When extra standard mixtures are used and more absorbances are measured, the precision of the calibration would be increased. The least square estimate of K, therefore, takes the form

$$K = (C^{\mathrm{T}}C)^{-1}C^{\mathrm{T}}A \quad (1)$$

provided that $\mathrm{R} \geq \mathrm{N}$, where R is the number of solutions. Once K has been calculated and the absorbances of the unknown system have been measured, $\hat{C}$ can be calculated from

$$\hat{C} = (K^{\mathrm{T}}K)^{-1}K^{\mathrm{T}}\hat{A} \quad (2)$$

provided that $M \geq N$, M being the number of wavelengths. This is K-matrix representation of Beer's law. Interaction is assumed to be absent which is also evident from the good fit of this linear model.

2.2. Computer programme

A SNPC personal computer of Hinditron was used for data analysis. A programme in PASCAL language was developed by the authors for this purpose.

2.3. Instrumentation

A Hitachi 200-20 double beam spectrophotometer with 1-cm quartz cell was used for measuring absorbance.

2.4. Materials

Paracetamol RS; ibuprofen RS (RS-reference standard); Caplets of Ibuprofen 425 parts, paracetamol 325 parts, starch 72 parts, talk 4.5 parts and lactose 73.5 parts; sodium hydroxide A.R.; sodium hydroxide solution 0.1 (M).

2.5. Methods

For the determination of K, accurately weighed samples of ibuprofen (ca. 85 mg) and paracetamol (ca. 60 mg) were dissolved in 75 ml of sodium hydroxide (0.1 M) and the volume was made upto 100 ml by adding sufficient sodium hydroxide solution (0.1 M). A portion of this solution (1.0) was diluted to 100 ml with the same sodium hydroxide solution and the absorbances were measured at 225, 226, 228, 230, 232, 234 and 235 nm against water.

To determine the two drugs in tablets, an accurately weighed portion of the powdered tablet containing about 85 mg of ibuprofen was mixed well with 75 ml of sodium hydroxide solution (0.1 M) and the volume was made up to 100 ml with the same sodium hydroxide solution. The recommended procedure is to add known amounts of the drugs to a tablet powder containing no active ingredients (drugs). After filtration through Whatman No. 41 filter paper, 1.0 ml of the filtrate was diluted to 100 ml with sodium hydroxide solution (0.1 M) and the absorbances were measured exactly as described above.

Six samples of tablets manufactured by three different manufacturers were taken and for each sample triplicate determination were performed.

3. Choice of wavelengths

From the solutions of known concentration and the corresponding absorbances, the proportionality censtant matrix was derived. By using Eq. (1), error matrix was then determined by comparing actual absorbances and the calculated absorbances from known concentration using Eq. (2). At this point analysis of variance was used for testing and ordering of wavelengths. The wavelength which yields the highest '*F*' value is assigned top posittion thus representing the best wavelength position of the list and so on.

The second step involves use of three or more wavelengths so as to get the best estimate based on utilization of minimum number of wavelenghts. In our experiments choosing the seven wavelengths as mentioned above provided an excellent estimate.

4. Results and discussion

The individual spectra of the two drugs were shown in Fig. 1. Direct ultraviolet spectrophotometry could not be used to determine the two compounds individually in their mixtures but the least squares method seemed to offer great potential. The matrix proportionality constant $\underline{K}$ could be evaluated by applying Eq. (1) to measurements on the standard mixture at different wavelengths. After $\underline{K}$ was evaluated for a particular instrument, the contents of ibuprofen and paracetamol in tablets can be evaluated using Eq. (2). Results obtained for tablets prepared as described in Section 2 were as follows: for ibuprofen, the mean recovery from six samples of tablets was 100.39% (range 97.40–104.15%) with relative standard deviation (R.S.D.) of 2.61%, for paracetamol, the mean recovery was 98.54% (95.84–102.71%) with R.S.D. 2.68%.

The validity of Eq. (2) was tested further by adding known amounts of the drugs to a tablet powder without active ingredients. The results obtained by following the recommended procedure ware listed in Table 1. The mean recovery and R.S.D. for ibuprofen were found to be 99.47% and 0.77%. For paracetamol, the mean recovery and R.S.D. were 99.03% and 0.73 valid in the working ranges 4.0–24.1 μ ml^{-1} ibuprofen

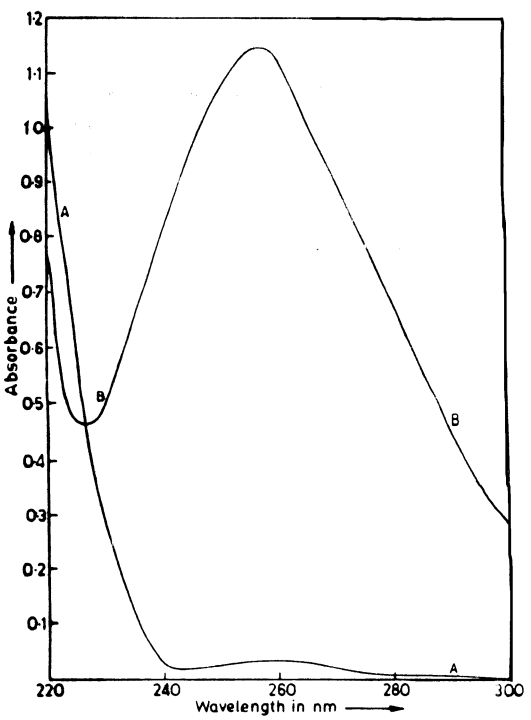

Fig. 1. Absorption spectra of A, 0.001682% m/V ibuprofen and B, 0.0001651% m/V paracetamol in sodium hydroxide solution (0.1 N).

Table 1
Recovery of ibuprofen and paracetamol added to tablet formation

Ibuprofen			Paracetamol		
Added (mg)	Found (mg)	Recovery (%)	Added (mg)	Found (mg)	Recovery (%)
99.60	99.90	100.30	125.60	124.20	98.88
	100.00	100.40	124.20	98.88	
124.50	122.80	88.63	157.00	156.80	99.87
	122.80	98.63	156.90	99.94	
149.40	148.60	99.56	188.40	185.20	98.30
	148.60	99.46	185.20	98.30	

and 3.0–19.6 μ ml^{-1} paracetamol in the standard solutions. These results showed that this method is sufficiently accurate and precise for validation. The contents of the two drugs in tablets were determined simultaneously in the presence of common excipients.

5. Conclusions

The titrimetric method for simultaneous determination of ibuprofen and paracetamol required titration twice, once against sodium carbonate solution using phenol red as indicator and again against sodium nitrite after diazotisation of paracetamol. Least squares method on the other hand offered an efficient method for determination of both compounds simultaneously thus reducing time. Added to these, the present method also offered many advantage over HPLC methods as the sample preparation with the proposed least square method was found to be much simpler and the instrument for operation could be available easily costing less. The method described herein, therefore, was found to be extremely simple, rapid and highly reliable for assay of commercial ibuprofen-paracetamol tablets without prior separation.

Although in the figure the wavelength scale is from 220 to 300 nm we have considered the wavelength range 220–240 nm because beyond 240 nm the absorbances of ibuprofen is practically insignificant. A total of 7 wavelengths quoted in the article were derived from the choice of wavelengths as described earlier.

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