Pakistan Journal of Pharmaceutical Sciences
Vol. 18, No.4, October 2005, pp.1-6

SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF IBUPROFEN IN TABLETS

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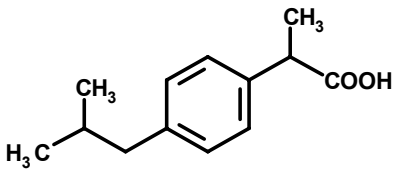
Ibuprofen in film coated tablets of different strengths has been determined using different spectrophotometric methods. These are: (i) the compensation method, (ii) a two wavelengths method, (iii) second-order and (iv) fourth-order derivative methods, and (v) a curve fitting method based upon computing the quadratic coefficient of the orthogonal polynomials expansion of its benzenoid absorption characteristics. All results were compared with the HPLC method of the B.P. 2003 using paired comparison. Developed methods have been validated and applied to different tablet formulations. Mean differences from the B.P. method were found to be -0.10, -0.30, -0.10, -0.16, -0.34 %, respectively. In view of the relatively low specific absorbance of ibuprofen in the ultraviolet region [A (1%, 1cm) =18.5 at 264 nm] its accurate and precise determination in different tablet formulations is challenging due to the presence of interferences from excipients.

Keywords: Ibuprofen, NSAID, derivative spectrophotometry, tablets, curve fitting, compensation method, chemometrics.

INTRODUCTION



Ibuprofen
(±)-2-(4-isobutylphenyl)propionic acid
$C_{13}H_{18}O_2$
Mol. wt. 206.28

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effect is due to its inhibitory action on cyclo-oxygenases which are involved in the biosynthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever. Its main adverse effects are gastro-intestinal disturbances.

Ibuprofen is official in the B.P. 2003 and the U.S.P. 27 NF 22.

The U.S.P. method for the determination of ibuprofen and its tablets is by HPLC, using chloroacetic acid/acetonitrile as mobile phase, L1 column, valerophenone solution as an internal standard and a flow rate 2 ml/min and measuring response at 254 nm. A titrimetric method for ibuprofen determination and an HPLC method for the tablets using methanol/H_2O/o-phosphoric acid as mobile phase, C18 column, flow rate is 1.5 ml/min and detection wavelength of 264 nm are recommended by the B.P. 2003. Spectrophotometric methods for the determination of ibuprofen have also been published. A mixture of ibuprofen and methocarbamol has been determined in tablets using two wavelengths method (Satheesh-Manikandan *et al.,* 2001).

First derivative spectrophotometry has been applied to the determination of mixtures of ibuprofen and dextropropoxyphene (Sachan and Trivedi, 1998) and paracetamol (Basu *et al.,* 1998) in solid dosage forms. Ibuprofen has also been determined in tablets through its copper complex (El-Raghy *et al.,* 1994).

EXPERIMENTAL

Materials

Ibuprofen (B.P. 2003) supplied from SPIMACO,(Qassim, Saudi Arabia), brufen tablets 200 mg (Knoll AG., Ludweghaven, Germany), ultrafen tablets 200mg, 400 mg, 600 mg (Glaxo Wellcome, Egypt), sabofen tablets 600 mg (SPIMACO).

Solvent

The solvent was prepared from a mixture of 3 volumes orthophosphoric acid: 247 volumes of water: 750 volumes of methanol.

Apparatus

A Perkin Elmer Lambda EZ201 UV/Vis spectrophotometer with 1-cm quartz cuvettes. The device is connected to a panasonic impact dot matrix printer 24 pin KX-P 3626.

Standard solution
Ibuprofen standard solution (2.0 mg/ml) was prepared in the above mentioned solvent.

For HPLC measurements: the stock solution was injected into a C18 column at flow rate of 1.5 ml/min at ambient temperature. A volume of 1.00µL was injected and detected at 264 nm.

For UV measurements: aliquot volumes of 4 to 14ml (in 2-ml steps) of standard ibuprofen solution were transferred into 100-ml calibrated flasks and diluted to volume with the same solvent to contain final concentrations of 80 to 280 µg/ml, respectively. Absorption curves were recorded over the wavelength range 220-300nm at 2-nm intervals at scan speed 100 nm/min.

Procedures
Ten ibuprofen tablets of each product were accurately weighed, ground and mixed well. A quantity of the resulted powder equivalent to about 200 mg ibuprofen was accurately weighed and transferred into 100-ml calibrated flasks using the prepared solvent. The flasks were sonicated for 30 minutes and dilutions were completed to volume. The tablets extracts were then centrifugated at 2500 rpm for 5 min.

For HPLC measurements: the centrifugate was injected into a C18 column at a flow rate of 1.5 ml/min and detection wavelength of 264 nm.

For UV measurements: aliquot volumes of 4 to 14ml (in 2-ml step) of stock solutions were transferred into 100-ml calibrated flasks and diluted to volume with the same solvent to contain final concentrations of 80 to 280 µg/ml. The absorbance (zero-order) and the absorbance difference of sample vs. reference (compensation method) were recorded for each solution at 2-nm intervals over the wavelength range 220-300nm at scan speed 100 nm/min.

RESULTS AND DISCUSSION

Application of the compensation method
The compensation method is a non-mathematical method, which despite the need for personal judgment, is very useful in practice. The irrelevant absorption curve is assumed to possess the simplest possible shape and none of the characteristics of the pure compound.

The compensation method involves a comparison of several difference spectra, (sample-reference) using different concentrations of reference substance in the reference cell. Thus, if A_s and A_r refer to the absorbance of the relevant cells against air for sample and reference,

$$\Delta A = A_s - A_r \qquad (1)$$

The pure compound characteristic peak, which may be seen in the ΔA curve, gradually diminishes as C_r increases, finally disappearing at the balance point, for which $C_r = C_s$. Further increase in C_r then leads to an over-compensated difference curve which bears an inversion of the pure compound's characteristic peak (figure 1). The difference curve at the balance point coincides with the irrelevant absorption present. The accuracy of the method in the assay of single and multi-component mixtures depends upon correct evaluation of the balance point. The method has been successfully applied to the determination of single component in the presence of interference arising from either additives or degradation products. The compensation method has been computerized (Wahbi *et al.,* 1989) to facilitate its application.

Ibuprofen has been determined in tablets using the compensation method. The method has also been used to reveal the presence and shape of irrelevant absorption due to tablet excipients. The latter has been detected at the balance point. Table 1 shows the results obtained for the determination of ibuprofen in five tablet formulations using the compensation method. In all cases the results obtained were found to be within ±5% of the labeled quantity and therefore

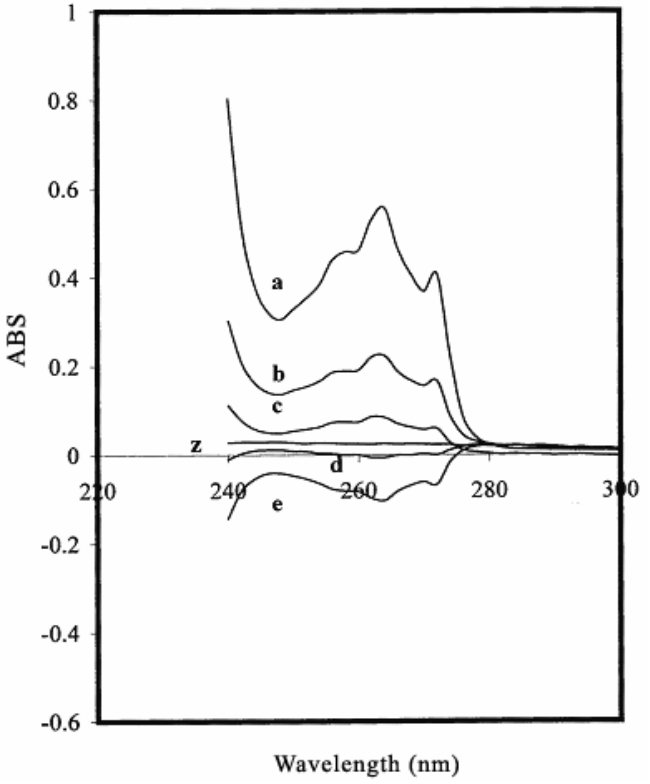


Fig. 1: Application of the compensation method to the determination of ibuprofen in product C, (Ultrafen 400 mg) tablets., (a) gross curve, (b) and (C) difference curves obtained by compensation, (Z) the balance point = irrelevant absorption curve, (d) and (e) over compensated curves.

fulfill the requirements of the B.P. 2003 (±5%) and the USP specifications (±10%). The irrelevant absorption curve obtained at the balance point in all cases was found to be very simple (figure 1). It could be described as a constant or very slightly linear sloping over the wavelength range 250 up to 280 nm.

This may suggest the use of other simple mathematical (or chemometric) methods that can eliminate the presence of such interference during spectrophotometric determinations of these tablets. Figure 1 shows the practical steps for the application of the compensation method. Common tablet fillers that could be present with these tablets such as hydroxypopyl cellulose, Avicel PH 101, sodium lauryl sulphate, Avicel PH 102, croscarmellose sodium and purified talc have been investigated to determine their absorption characteristics over the wavelength range 240 to 280 nm. It was found that these tablet fillers when extracted with the solvent showed negligible absorption characteristics over the wavelength range 240 to 280 nm. The irrelevant absorption revealed by the compensation method could be due to excipients unknown to us. It should be corrected for in order to obtain accurate results for the determination of ibuprofen.

Application of the absorbance difference at two wavelengths method (Elimination of constant interference)

An irrelevant absorption which is a constant function of wavelength can be corrected for by measuring the difference A_{s1}-A_{s2} where s_1 and s_2 denotes sample, at λ_1 and λ_2, respectively. Hence

$$C_s\,(A_{s1}-A_{s2}) = (A_{r1}-A_{r2})\,C_r \qquad (2)$$

where r_1 and r_2 stand for pure substance, at λ_1 and λ_2, respectively. Accordingly,

$$C_s = \frac{A_{s1}-A_{s2}}{Ar_1-Ar_2} \times C_r \qquad (3)$$

This is the simplest method for the elimination of a constant interference under the assumption that the interference curve is a constant function of wavelength. The irrelevant absorption curves revealed by the compensation method proved to be almost a constant function of wavelength in the different brands of tablets. Accordingly, the absorbance difference at (two wavelengths) was suggested as a method of analysis in order to eliminate the contribution of such interference to A_{max} at 264 nm. The two selected wavelengths were 264 and 280 nm.

Table 1
Collective table for the validation of the assays used for the determination of ibuprofen in tablets using the different methods

Validation Parameters						
Method*						
Parameters		ΔA	D_2	D_4	C	HPLC B.P. 2003
Correlation coefficient,	r	0.9997	0.9999	0.9998	0.9998	0.9997
Intercept,	a	-0.0048	-0.0018	-0.0006	-0.0114	0.0088
Slope,	b	0.001809	0.00080	0.00063	0.00243	7.36
Standard deviation , S_a		4.15E-03	1.2E-03	1.3E-03	4.8E-03	0.017
Standard deviation, S_b		2.2E-05	6.42E-06	6.73E-06	2.5E-05	0.09
LOD µg/ml		7.57	4.95	6.81	6.52	
LOQ µg/ml		22.94	15.0	20.63	19.75	
Accuracy**	Mean of %found	99.9	100.6	100.6	99.6	
	C.V.% of % found	0.82	0.85	1.60	0.80	
Precision+	C.V.% of Repeatability	0.68	1.27	1.29	1.24	

*Linearity range = 80 – 280 µg / ml
**6 separate determinations (160 – 240 mg added to tablet fillers)
+Triplicate assays for the three concentrations 80, 160 and 280 µg/ml i.e. 9 results.
LOD = Limit of Detection, LOQ = Limit of Quantitation.

The absorbance difference at two wavelengths has been applied to the determination of ibuprofen in tablets. The maximum wavelength at 264 nm was selected and the second wavelength was 280 nm, where ibuprofen showed negligibly low absorbance contribution. The results obtained are shown in table 1. The mg of ibuprofen per tablet was found to be within ±5% of the labeled amount. This complies with both the B.P. and the USP specifications for ibuprofen in tablets.

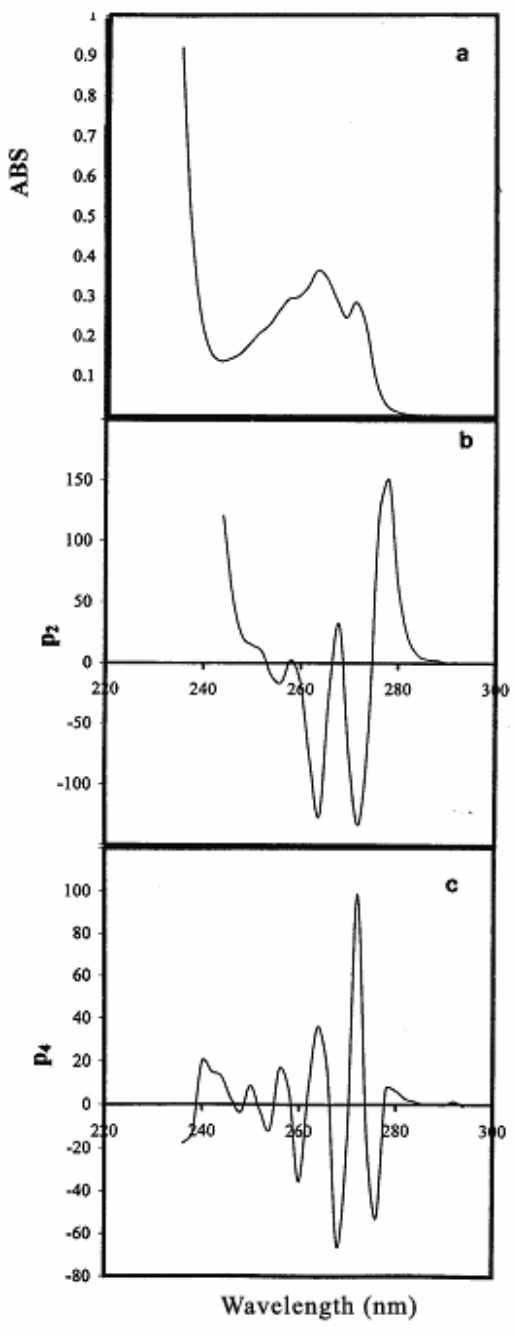


Fig. 2(a) Absorption curve of 200µg / ml of ibuprofen in the solvent, its D_2 (b) and D_4 (c) derivative curves.

Specificity

The absorption characteristics of the tablet solution with two maxima at 264 nm and 272 nm and a shoulder at 258 nm together with the compensation method explain the specificity of the method.

Linearity range

The absorbance difference at A_{264nm}-A_{280nm} for ibuprofen in the solvent used was found to be linearly related to concentration over the range 80 to 280 µg/ml. The regression analysis of the linear relationship is shown in table 2.

Application of derivative spectrophotometry

Second and fourth order derivative curves of ibuprofen have been recorded (figure 2) using a Visual BASIC (Hamdy, 2004) program to obtain the corresponding derivative curves (Wahbi, 1991). The second order, D_2 curve was found to possess optima at the mean wavelengths 265, 273 and 281 nm. The fourth order, D_4 curve was found to possess optima at the mean wavelengths 267, 271, 277 and 279 nm.

Table 1 shows the results obtained for the determination of ibuprofen in tablets using second and fourth order derivative curves at the selected optima. The results were found to be within ±5% of the labeled amount (table 1).

Specificity

The D_2 and D_4 curves for tablet solutions and reference solutions of ibuprofen in the solvent used were found to be coinciding with each other (within ± 1nm) with regard to position of optima (figure 2).

Linearity

D_2 at 265 nm and D_4 271 nm for ibuprofen were found to be linearly related to concentration over the concentration range 80 to 280 µg/ml. Regression analysis of the linear relationship is shown in table 2.

Application of a curve fitting method and principle

An absorption curve $f(\lambda)$ can be represented as a polynomial equation of the form:

$$f(\lambda) = A + B\lambda + C\lambda^2 + D\lambda^3 + E\lambda^4 + \ldots\ldots\ldots \quad (4)$$

where A, B, C, D, E etc are the coefficients of the constant, linear, quadratic, cubic, quartic etc components of the absorption curve, respectively. The curve fitting process is carried out to minimize the error, e, in the difference

$$f(\lambda) - [A + B\lambda + C\lambda^2 + D\lambda^3 + E\lambda^4 + \ldots\ldots] = e \quad (5)$$

Calculating the coefficient, C, of the quadratic term $C\lambda^2$ will be highly representing an absorption curve quadratic in nature, and will not be affected by the constant or linear irrelevant absorption. BASIC programs are available that

facilitate the calculation of C, or any other required coefficient from a set of absorbance measurements at a defined set of wavelengths (Wahbi, 1993). The coefficient, C, is linearly related to concentration, highly reproducible, specific to the analyzed compound and independent of constant and linear components of the substance absorption curve and irrelevant absorption curve. Using a standard ibuprofen solution with concentration C_s, the concentration of the tablet solution C_t can be obtained.

Choice of wavelengths

Certain wavelengths in the absorption curve of ibuprofen have been selected. These points were chosen to coincide with the maxima, minima and shoulders of the absorption characteristics of ibuprofen. These were: 243, 249, 254, 258, 261, 264, 269, 272 and 273nm. A curve fitting BASIC program has been applied to calculate the quadratic coefficient, C.

Ibuprofen in tablets has been determined using the above mentioned curve fitting process at the selected wavelengths. The results obtained are shown in table 1. The results obtained were found to be within ±5% of the labeled amount.

Specificity

The absorption curve of the tablet solution was found to possess two maxima at 264 and 272nm and a shoulder at 258 nm. This coincides with the absorption characteristics of ibuprofen. Furthermore, the compensation technique proved that interferences were found to be a non- specific constant curve.

Linearity

The coefficient of the quadratic term, C for ibuprofen was found to be linearly related to concentration over the concentration range 80 to 280 µg/ml. The regression analysis of the linear relationship is shown in table 2.

Application of the B.P. 2003 HPLC reference method for the determination of ibuprofen in tablets

The HPLC method of the B.P. 2003 has been applied to assay ibuprofen in tablets. Solutions of ibuprofen standard and tablets of concentration 0.2% w/v were prepared and analyzed.

Retention times of ibuprofen for sample and reference solutions were found to be 4.50 and 4.51 min, respectively. This confirms identification and specificity of ibuprofen. Table 1 shows the results obtained for the analysis of

Table 2

Collective table for the determination of ibuprofen in tablets using different methods and paired comparison

% Found per tablet						
Method						
Product	Compensation	ΔA	D_2	D_4	C	HPLC
A	100.7	100.8	101.7	101.1	100.4	103.3
B	99.7	99.0	99.7	99.4	99.5	98.1
C	99.2	98.2	98.5	98.5	98.9	98.2
D	97.2	98.6	97.7	98.4	97.6	99.3
E	103.0	102.2	102.2	102.1	102.2	101.4
Mean of differences*	-0.1	-0.3	-0.1	-0.16	-0.34	
S.D. of difference	2.08	1.39	1.45	1.40	1.86	
S.E. = S.D.√5	0.93	0.62	0.65	0.62	0.83	
Confidence++ limits	± 2.4	± 1.6	± 1.7	± 1.6	± 2.1	

*Difference between % found of each method and the HPLC method for each product.

tablets. The results obtained are within ±5% of the labeled amount. This complies with the B.P. specifications for ibuprofen tablets.

STATISTICAL ANALYSIS

Paired comparison between the results obtained for the determination of ibuprofen in tablets using different method

The different spectrophotometric methods applied to the determination of ibuprofen in tablets gave satisfactory results conforming to official requirements. However, it was deemed necessary to carry out paired comparison (Davis and Goldsmith, 1972) test to compare these results with those obtained using the reference HPLC method. Table 1 shows the collective data for the results obtained and their statistical analysis.

Assay validation

Assay validation of all the above mentioned procedures have been carried out according to the USP 27 NF 22 and BP 2003 requirements. Thus, linearity range has been specified. The accuracy and precision have been proved. Limit of Detection (LOD) and Limit of quantitation (LOQ) have been calculated (table 2). All assays fulfill Category I assays of the USP.

CONCLUSION

Table 1 shows that the absorbance difference at two wavelengths ΔA, the D_2, the D_4, and the curve fitting, C, methods gave results that are -0.3 ± 1.6%, -0.1 ± 1.7%, -0.16 ± 1.6%, and -0.34 ± 2.1% of the HPLC method, respectively. Accordingly, all the applied spectrophotometric methods gave satisfactory results for the determination of ibuprofen in tablets when compared with the HPLC method. The compensation method is a non-mathematical method that depends upon personal judgment of the balance point. The results obtained were found to be -0.1 ± 2.4% of HPLC method. The choice of any method depends upon the shape of the irrelevant absorption curve present in the sample solution. The two wavelengths ΔA method eliminates a constant interference. Both D_2 and D_4 methods are specific in their position of optima for test and standard and correct for a linear interference. The curve fitting method is also specific to ibuprofen but assumes that the irrelevant absorption is not quadratic. Results of the compenation method depend upon personal judgment. However, the method is mainly used to reveal the shape of the interference curve. All these spectrophotometric methods are rapid, precise and accurate to be applied during the manufacturing process and end product quality control. The position of optima and ratios of derivative curves calculated for D_2 and D_4 can be used for the identification of ibuprofen.

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