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Received May 4, 1998
Accepted June 5, 1998

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Fourier transform infrared spectrometric determination of paracetamol and ibuprofen in tablets

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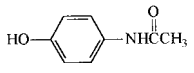
A fourier transform infrared (FTIR) spectrometric technique is described for the simultaneous determination of ibuprofen and paracetamol in two compositions of pharmaceutical tablets. Quantification was carried out by measuring the absorbances at 1684 and 1740 cm^{-1} for paracetamol and ibuprofen, respectively, using the baseline established at 1780 cm^{-1} for measurement correction. The linear correlations with high values of correlation coefficients (0.9999) were obtained at a concentration range of 2.0–10.0 mg ml^{-1} for both analytes. The detection limits were found to be 0.34 and 0.21 mg ml^{-1} for paracetamol and ibuprofen, respectively. A HPLC method was developed as reference method for the determination of both compounds. The results obtained from the FTIR technique are in good agreement with those from HPLC.

1. Introduction

Paracetamol (**1**) is an antipyretic and analgesic compound and ibuprofen (**2**) is a non-steroidal anti-inflammatory analgesic drug [1]. These two drugs are used in combination for the relief of moderate pains. The combined tablets are marketed under various trade names in two compositions, 325 mg of paracetamol and 200 mg or 400 mg of ibuprofen.



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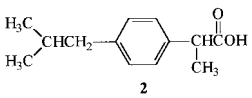

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Many methods have been reported for the determination of paracetamol [2–11] and ibuprofen [12–15]. The combined dosage forms of paracetamol and ibuprofen have been estimated by high performance thin layer chromatography [16] and gas-liquid chromatography [17, 18]. However, no data are available for the direct determination of paracetamol and ibuprofen combinations by FTIR. The goal of this work was to demonstrate an alternative FTIR technique for the simultaneous determination of paracetamol and ibuprofen in tablets which is simple, rapid, accurate and inexpensive.

2. Investigations, results and discussion

The absorbance of a C=O stretch is the interesting band for this study, since it is one of the most prominent band in the spectrum and both paracetamol and ibuprofen contain this group in their structures. Chlorinated solvents such as tetrachloromethane (CCl_4), dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) which are transparent in this region cannot be used as solvents for analysis. Ibuprofen can be dissolved in most of the organic solvents

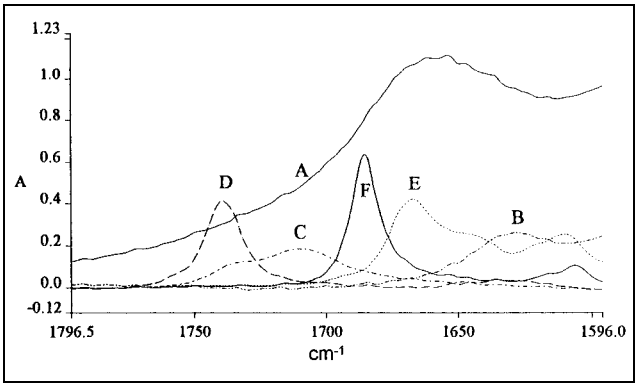

Fig. 1: Spectra of A, methanol; B, acetonitrile, and solvent subtracted absorbance spectra of C, ibuprofen 10 mg ml^{-1} in methanol; D, ibuprofen 10 mg ml^{-1} in acetonitrile; E, paracetamol 10 mg ml^{-1} in methanol; F, paracetamol 10 mg ml^{-1} in acetonitrile

including chlorinated ones, however, paracetamol is very slightly soluble in these solvents. In addition to solubility properties and transparency of the solvent in the region of interest, interactions of the solvent and the carbonyl function are important to consider for solvent selection.

When methanol was first used as solvent, a broad band appeared about 1710 cm^{-1} for ibuprofen as shown in Fig. 1. This is because the hydrogen bonding involving hydroxyl-carboxyl bonds occurs. In methanol, with the hydrogen bond to the carbonyl group, paracetamol gives the carbonyl stretch band at 1667 cm^{-1}. Both carbonyl bands of ibuprofen and paracetamol in methanol are broad and overlapped as shown in Fig. 1.

The solubility of paracetamol in acetonitrile is not as good as in methanol. However, both paracetamol and ibuprofen can be very well dissolved in acetonitrile at the concentration ranges of this study. To improve the band shapes and/or the overlapping of the carbonyl bands, acetonitrile was attempted since the interaction occuring with acetonitrile is different from that with methanol. When acetonitrile is used as a solvent, the carbonyl functions of both compounds are not hydrogen bonded and were shifted to higher frequencies. The carbonyl stretch bands of ibuprofen and paracetamol occur at 1740 and 1685 cm^{-1}, respectively. As seen in Fig. 1, the carbonyl bands of both paracetamol and ibuprofen are almost completely separated. At the same concentrations, the carbonyl bands of both compounds are most intense in acetonitrile than in methanol. Additionally, acetonitrile is more transparent than methanol in the region of interest.

Besides the carbonyl band, paracetamol gives a benzene ring vibration at 1515 cm^{-1} in both acetonitrile (Fig. 2) and methanol (Fig. 3). This band is very sensitive compared with the carbonyl band. Unfortunately, ibuprofen also gives a small band at this position. This band is therefore unsuitable for the determination of these combinations. In acetonitrile another band at 1249 cm^{-1} of paracetamol is not overlapped with any bands of ibuprofen, however, it is less sensitive than the carbonyl band.

For the determination of these combined drugs, acetonitrile was chosen as the solvent. The acetonitrile spectrum was subtracted from the sample spectrum using a substraction factor of 1. Quantification analysis was then carried out by measuring absorbance of the carbonyl bands at 1684 and 1740 cm^{-1} for paracetamol and ibuprofen, respectively, with baseline corrected at 1780 cm^{-1}.

The linear regression equations and the statistical evaluation of the calibration plots are listed in Table 1. Under the experimental conditions described above, linear correlations with high values of correlation coefficients (0.9999) were obtained at the concentration range of 2.0–10.0 mg ml^{-1} for both paracetamol and ibuprofen. The detection limits obtained from the sensitivity of the calibration graph and for $3s_b$ (s_b = standard deviation of a blank) were found to be 0.34 and 0.21 mg ml^{-1} for paracetamol and ibuprofen, respectively.

The interference effects of tablet excipients and drugs were investigated by preparing mixtures of paracetamol, ibuprofen and typical tablet excipients as shown in Table 2 and analysing these mixtures with the proposed method. The good recoveries obtained (Table 2) for both paracetamol and ibuprofen demonstrate the specificity and accuracy of the described method. In addition, the relative standard deviations for five determinations are satisfactorily low indicating the good reproducibility of the proposed method.

A HPLC method was developed as the reference method for the FTIR technique. The mobile phase was chosen after several trials of acetonitrile/water in various proportions and different pH values. The change in the wavelength of detection during the run was performed to achieve maximum detector response for both drugs. The chromatographic system described allows complete baseline separation with the retention times of 2.24 and 3.15 min for paracetamol and ibuprofen, respectively. The linearities of the detector responses were determined at the concentration ranges of 3.0–15.0 μg ml^{-1} of paracetamol and 2.0–12.0 μg ml^{-1} of ibuprofen, respectively. The fol-

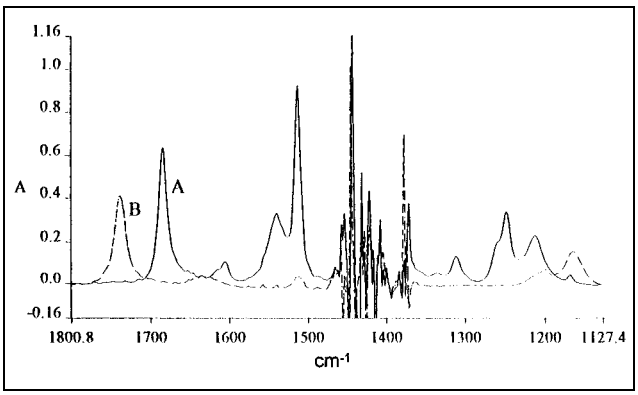

Fig. 2: Solvent subtracted absorbance spectra of A, paracetamol 10 mg ml^{-1} in acetonitrile; B, ibuprofen 10 mg ml^{-1} in acetonitrile

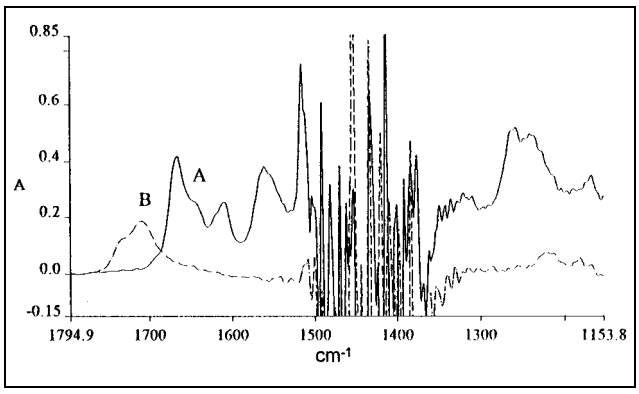

Fig. 3: Solvent subtracted absorbance spectra of A, paracetamol 10 mg ml^{-1} in methanol; B, ibuprofen 10 mg ml^{-1} in methanol

Table 1: Calibration equations for the determination of paracetamol and ibuprofen

Compound	Range (mg · ml^{-1})	Calibration equation[a]	r[b]	DL[c] (mg · ml^{-1})
Paracetamol	2.0–10.0	$A = 0.01414\ (\pm 0.0036) + 0.06105\ (\pm 0.0008)\ C$	0.9999	0.34
Ibuprofen	2.0–10.0	$A = -0.00162\ (\pm 0.0093) + 0.04076\ (\pm 0.0017)\ C$	0.9999	0.21

[a] Each calibration graph was obtained from 7 experimental points, average of 5 determinations
[b] Correlation coefficient
[c] Detection limit

Table 2: Determination of paracetamol and ibuprofen in a synthetic mixture

Mixture	Added concentration (mg ml^{-1})			Recovery ± sd (%)	
	Paracetamol	Ibuprofen	Excipient	Paracetamol	Ibuprofen
1	5.0	3.0	3.0	102.13 ± 0.75	99.45 ± 0.10
2	5.0	5.0	3.0	101.23 ± 0.52	99.36 ± 0.60
3	8.0	3.0	3.0	98.96 ± 0.24	98.16 ± 0.24
4	8.0	5.0	3.0	98.51 ± 0.23	100.26 ± 0.09
5	5.0	3.0	5.0	102.71 ± 0.80	100.22 ± 0.45
6	5.0	5.0	5.0	102.39 ± 0.39	100.91 ± 0.29
7	8.0	3.0	5.0	99.35 ± 0.17	99.89 ± 0.35
8	8.0	5.0	5.0	98.58 ± 0.01	99.32 ± 0.23
9	6.5	4.0	4.0	99.85 ± 0.08	100.64 ± 0.31
10	3.6	4.2	3.0	98.98 ± 0.36	101.57 ± 0.77
12	3.6	7.0	3.0	98.57 ± 0.17	101.29 ± 0.81
11	6.0	4.2	3.0	99.86 ± 0.25	100.48 ± 0.48
13	6.0	7.0	3.0	100.31 ± 0.17	99.98 ± 0.53
14	3.6	4.2	5.0	100.36 ± 0.42	100.87 ± 0.55
16	3.6	7.0	5.0	97.22 ± 0.09	100.68 ± 0.20
15	6.0	4.2	5.0	99.34 ± 0.44	101.23 ± 0.37
17	6.0	7.0	5.0	100.02 ± 0.53	100.35 ± 0.35
18	4.8	5.6	4.0	98.41 ± 0.06	100.78 ± 0.25

* Values are the average of five determinations ± the corresponding standard deviation

Table 3: Comparison of FT-IR and HPLC values for the determination of paracetamol and ibuprofen in commercial tablets

Sample	Recovery ± sd (%)[b]			
	Paracetamol		Ibuprofen	
	FT-IR	HPLC	FT-IR	HPLC
Brand I[a]	104.98 ± 0.41	104.39 ± 0.66	102.43 ± 0.64	103.54 ± 1.24
	t = 1.68		1.99 (2.31)[c]	
	F = 0.81		1.78 (6.39)[c]	
Brand II[a]	100.48 ± 0.96	100.26 ± 0.61	95.06 ± 0.82	95.82 ± 0.94
	t = 0.42		0.04	
	F = 5.16		1.37	

[a] Brand I containing 325 mg of paracetamol and 200 mg of ibuprofen per tablet, Brand II containing 325 mg of paracetamol and 400 mg of ibuprofen per tablet.
[b] Values indicated are the average of five determinations ± the corresponding standard deviation; percentage recovery from the label claim amount
[c] Values in parentheses are the theoretical values at p = 0.95

lowing linear equations were obtained through regression analysis: A = 110483.70C + 9850.00 (r = 0.9999) for paracetamol; and A = 111270.00C − 1286.50 (r = 0.9998) for ibuprofen, where A is peak area, and C is the drug concentration.

The accuracy of the FTIR method was also tested by analysing two brands of commercial tablets which contain 325 mg of paracetamol, 200 mg of ibuprofen and 325 mg of paracetamol, 400 mg of ibuprofen. The results obtained are summarized in Table 3 and compared to those with the HPLC method. The calculated t- and F-tests in the determinations of both brands do not exceed the theoretical values at the 95% confidence level, indicating no significant difference between the two methods and demonstrating the utility of the purposed method for the simultaneous determination of both drugs.

3. Experimental

3.1. Materials and equipment

A Perkin-Elmer (Norwalk, CT, USA) Model 1620 FTIR spectrometer, equipped with a deuterated triglycine sulfate (DTGS) detector, was employed to carry out the absorbance measurements, with a resolution of 4 cm^{-1}. The spectra were obtained using a demountable pathlength liquid sampling cell with a CaF_2 windows and a 0.1 mm polyethylene spacer. The spectra were collected with accumulating 20 scans. A single-beam spectrum of the empty cell was recorded as the background spectrum. Solvent subtraction, baseline correction and the measurement of absorbance were performed using Spectrum Lite software (Perkin-Elmer, Norwalk, CT, USA).

The high-performance liquid chromatograph consisted of a Waters 600 E pump controller, Waters 486 UV detector, and Waters 746 Data Module (Waters Corporation, Milford, MA, USA). Chromatographic separation was carried out at ambient temperature on a Hypersil BDS phenyl column (5 μm particles, 4.6 × 150 mm) (Shandon HPLC, London, England). A Rheodyne injector model 7125 was used to load and inject the samples. The compounds were separated isocratically with a mobile phase consisting of CH_3CN/0.1 M-KH_2PO_4 (pH 6.5) (35 : 65 v/v). The flow rate was 1 ml min^{-1}. The injection volume was 20 μl and the detector wavelength was set at 225 nm.

Paracetamol was obtained from Aldrich (Milwaukee, WI, USA) and ibuprofen was supplied by Sigma (St. Louis, MO, USA). All other reagents employed were of analytical reagent grade. Two commercial tablets containing 325 mg of paracetamol, 200 mg of ibuprofen and 325 mg of paracetamol, 400 mg of ibuprofen were bought in Thai pharmacies.

3.2. Preparation of calibration solutions

All stock solutions were prepared by dissolving appropriate amounts of the compounds in CH_3CN or the HPLC mobile phase. Working standards for FTIR analysis were prepared by an appropriate dilution of the stock solutions in CH_3CN to obtain a concentration range of 2.0–10.0 mg ml^{-1} for both paracetamol and ibuprofen. For HPLC analysis, the stock solutions were diluted with mobile phase solution to obtain concentration ranges of 3.0–15.0 μg ml^{-1} of paracetamol and 2.0–12.0 μg ml^{-1} of ibuprofen, respectively.

3.3. Preparation of test samples

For the interference study, mixtures of paracetamol, ibuprofen and a typical tablet excipient (containing corn starch, lactose, PVP K-30, magnesium stearate, and talcum), in CH_3CN were prepared. Two sets of 2^3 full factor-

ial design were built, the nominal concentrations at the center points of which are the mixtures where drug components are close to the two compositions of commercial tablets (mixture 9 and 18 in Table 2). In the other mixtures, the concentrations are varied to correspond to about ±25% of their respective nominal concentrations at the center points. The concentration ranges chosen were in the linear concentration ranges of this study and were quite wide in order to make certain that each component does not interfere in the determination of each drug. The concentrations of the various components in set I (mixtures 1–9) and set II (mixture 10–18) are given in Table 2.

For the determination of commercial tablets, 20 tablets were ground to fine powder after determination of the average mass. An amount of powder equivalent to 245 mg of paracetamol was weighed into a 25 ml stoppered calibrated flask, and 20 ml of CH_3CN were added. After shaking in an ultrasonic bath for 15 min, the solution was made up to volume with CH_3CN.

After filtration through a filter paper, the first portions were discarded, and 5 ml of the filtrate was diluted to 10 ml with CH_3CN. This solution was analysed by the FTIR method. For HPLC analysis, 1 ml of the filtrate was diluted to 50 ml with mobile phase solution, and 2 ml of the resulting solution was further diluted to 25 ml with the same solvent.

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Received June 10, 1998
Accepted July 5, 1998

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