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Determination of ibuprofen and naproxen in tablets

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Abstract

Ibuprofen and naproxen have been quantified in tablets by capillary isotachophoresis. Hydrochloric acid (10 mmol/l) adjusted with creatinine to pH 5.0 plus 0.1% polyvinylpyrrolidone was used as the leading electrolyte and 10 mmol/l 4-morpholineethanesulfonic acid as the terminating electrolyte. Linearity was observed from 40.0 to 200.0 mg/l of ibuprofen (naproxen), with a coefficient of determination (r^2) of 0.999. Good quantitation was obtained in short analysis time. The isotachophoretic results were compared with those obtained by the fluorescence spectrometry. Experimental parameters for ibuprofen were: $\lambda_{EX} = 224$ nm and $\lambda_{EM} = 290$ nm. Experimental parameters for naproxen were: $\lambda_{EX} = 230$ nm and $\lambda_{EM} = 355$ nm. The calibration plot was found to be linear in the range 0.4–2.4 mg/l for ibuprofen and 5.0–20.0 μg/l for naproxen. The minimal sample pretreatment and relatively low running cost make isotachophoresis a good alternative to existing methods. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Capillary isotachophoresis; Fluorescence spectrometry; Ibuprofen; Naproxen

1. Introduction

Ibuprofen, [(*R*,*S*)-α-methyl-4-(2-methylpropyl)-benzeneacetic acid], is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of pain and inflammation in rheumatic disease and other musculoskeletal disorders [1]. Naproxen, [(*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid], is another member of this group of NSAIDs. It is widely used in the treatment of osteo- and rheumatoid arthritis and for the relief of mild to moderate pain [2]. A variety of methods are available in the literature for the determination of these compounds in pure form or pharmaceutical formulations including potentiometric titration [3], flow-injection analysis-FT-IR [4], high-performance liquid chromatography [5,6], supercritical fluid chromatography [7] for ibuprofen and spectrofluorimetry [8] for naproxen. Until now, liquid chromatography has been the major technique used for the determination of ibuprofen and naproxen in tablets. The same technique was also applied to collect the data in the United States Pharmacopoeia monograph on ibuprofen [9] and naproxen [10]. Re-

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cently, capillary electrophoresis (CE) has gained in interest, with growing attention to NSAIDs analysis in general [11–13]; conditions for the determination of ibuprofen [14–16] and naproxen [14,17,18] in a tablet dosage form have been described. CE offers an alternative technique; however, there is a general lack of acceptance of CE as a routine analytical tool, particularly in the regulatory environment. The high resolution which may be attained with CE has been shown to be especially useful for stereoselective determination of *S*-naproxen in tablets [18]. In addition, micellar electrokinetic capillary chromatography offers a fast separation with complete resolution between ibuprofen, codeine and their nine potential degradation products and excipients [16].

In our country recommended methods for ibuprofen and naproxen are European Pharmacopoeia methods. In European Pharmacopoeia the titrimetric methods with sodium hydroxide in methanol using phenolphthalein as chemical indicator are described for the routine determination of ibuprofen [19] and naproxen [20] in pure form. The utilization of chemical indicators for the indication of the end-point of the titration in the presence of coloring or insoluble excipients in tablets is fairly problematic.

The aim of the present contribution was to develop a isotachophoretic method for the determination of ibuprofen and naproxen in tablet dosage form as an alternative to the above-mentioned methods. The isotachophoresis is a simple, quick and low-cost method and therefore well suited for main drug determination. We have compared this method with fluorescence spectrometry.

2. Experimental

2.1. Instrumentation

2.1.1. ITP

A ZKI 02 isotachophoretic analyzer (Villa Labeco, Slovak Republic) equipped with a conductivity detector and a separation capillary (90×0.8 mm i.d.) was used. The driving current was 250 μA.

Hydrochloric acid (10 mmol/l) adjusted with creatinine to pH 5.0 plus 0.1% polyvinylpyrrolidone was used as the leading electrolyte (LE) and 10 mmol/l 4-morpholineethanesulfonic acid as the terminating electrolyte (TE).

2.1.2. Fluorescence spectrometry

All fluorescence measurements were done on a Perkin-Elmer LS 50 Luminescence spectrometer equipped with a xenon discharge lamp (20 kW) and 1×1 cm quartz cell. The LS 50 spectrometer was interfaced with an Epson PC AX2 microcomputer supplied with FL Data Manager Software (Perkin-Elmer) for spectral acquisition and subsequent manipulation of spectra. Experimental parameters for ibuprofen were: $\lambda_{EX} = 224$ nm, $\lambda_{EM} = 290$ nm and slit with 3.0 nm. Experimental parameters for naproxen were: $\lambda_{EX} = 230$ nm, $\lambda_{EM} = 355$ nm and slit with 3.0 nm.

2.2. Chemicals and samples

Hydrochloric acid, sodium hydroxide and polyvinylpyrrolidone (PVPD) were obtained from Lachema, creatinine and 4-morpholineethanesulfonic acid (MES) from Merck. Ibuprofen and naproxen were obtained from Sigma.

Stock solutions (800 mg/l) were prepared by dissolving 200.0 mg of the active compounds with 50 ml of 0.02 mol/l NaOH, and then diluting with distilled water into a 250.0-ml volumetric flask. These solutions were finally diluted either with water before the ITP measurements or with 0.05 mol/l NaOH before the fluorescence measurements. Ibuprofen and naproxen do not show alternations when using water and/or alkaline solutions as a solvent [21]. According to Hercegová et al. [22], ibuprofen and naproxen are stable in the leading electrolyte solutions used.

The Ibuprofen was labeled as containing 200 mg or 400 mg ibuprofen, corn starch, stearin, colloidal silicon dioxide, carboxymethyl starch-sodium salt, hydroxypropylmethylcellulose, titanium dioxide, erythrosin and silicone emulsion.

The Naprosyn was labeled as containing 250 mg naproxen, lactose and yellow pigment E 102 (i.e. tartrazine).

2.3. Calibration curve

Solutions for the ITP calibration curve were prepared by appropriate dilution of the stock solution with water. The concentration range was 40.0–200.0 mg/l; five standard solutions were prepared. Thirty microliters was injected into the ITP capillary.

Solutions for the fluorescence calibration curve were prepared by appropriate dilution of the stock solution with NaOH 0.05 mol/l. The concentration range was 0.4–6.4 mg/l for ibuprofen and 5.0–30.0 μg/l for naproxen. For each concentration range seven standard solutions were prepared.

2.4. Sample preparation

2.4.1. ITP

In all cases it was assumed that the actual content of the tablet corresponds to that reported by the manufacturing laboratories.

Five tablets were weighed and ground. An amount of the powder, equivalent to one average dragee, was transferred to a 250.0-ml volumetric flask, mixed with a 50 ml of 0.02 mol/l NaOH and then made with water up to 250.0 ml volume. The sample was centrifuged for 1 min at $3000 \times g$ and appropriate dilutions were made with water to a final concentration of 80 mg/l. Then 30 μl was injected into the ITP capillary.

2.4.2. Fluorescence spectrometry

Five tablets were weighed and ground. An amount of the powder, equivalent to one average dragee, was transferred to a 250.0-ml volumetric flask, mixed with a 50 ml of 0.02 mol/l NaOH and then made with water up to 250.0 ml volume. The sample was centrifuged for 1 min at $3000 \times g$ and appropriate dilutions were made with NaOH 0.05 mol/l to a final concentration of 1.6 mg/l for ibuprofen and 12.5 μg/l for naproxen.

2.5. Stress decomposition studies

Two 10.0-mg amounts of ibuprofen (naproxen) were transferred to two 250-ml flasks. Then, 100.0 ml of 1 mol/l NaOH were added to one of the flasks and 100.0 ml of 0.1 mol/l hydrochloric acid were added to the other. The two solutions were boiled under reflux for 36 h. The samples were collected at 24 h and 36 h. These solutions were then diluted either with 0.05 mol/l NaOH before the fluorescence measurements or with water before the ITP measurements. For the ITP, the solutions were finally neutralized with NaOH or with MES to pH 5. Thirty microliters of each solution was injected into the ITP system.

3. Results and discussion

3.1. ITP

The physicochemical properties of analytes, especially their low solubility in water and low mobility complicated the choice of a suitable electrolyte system. The isotachophoretic experiments showed that the pH of the leading electrolyte must be between 4.5 and 5.5 to ensure sufficient dissociation and effective mobility of the analytes [22]. The effect of pH was studied from 4.5 to 5.5 with 6-aminocaproic acid and from 5.0 to 5.5 with creatinine. In the pH range studied, the carboxylic group of analytes is dissociated and thus the analytes migrate as the anion. In the pH range 4.5–5.5, MES as one of the slowest anionic terminators works well and ensures a correct ITP migration. In more acidic electrolyte systems ($pH < 4.5$) there is a lack of suitable slow migrating terminators. At $pH > 5.5$ all analytes migrate in the terminator. Of several electrolyte tested, 10 mM creatinine hydrochloride-creatinine buffer (pH 5.0) and 10 mM MES solution were found to be the preferred leading and terminating electrolytes, respectively. The driving current applied to the capillary was 250 μA. The use of a higher driving current would be rather problematic because even the short capillary caused a high voltage value when run with MES as the terminating electrolyte in the system with a pH of 5.0. In Fig. 1 examples are given of the results of ITP experiments on (a) a standard solution of ibuprofen; (b) a sample solution prepared from the Ibuprofen tablet; (c) a standard solution of naproxen; and (d) a sample solution prepared

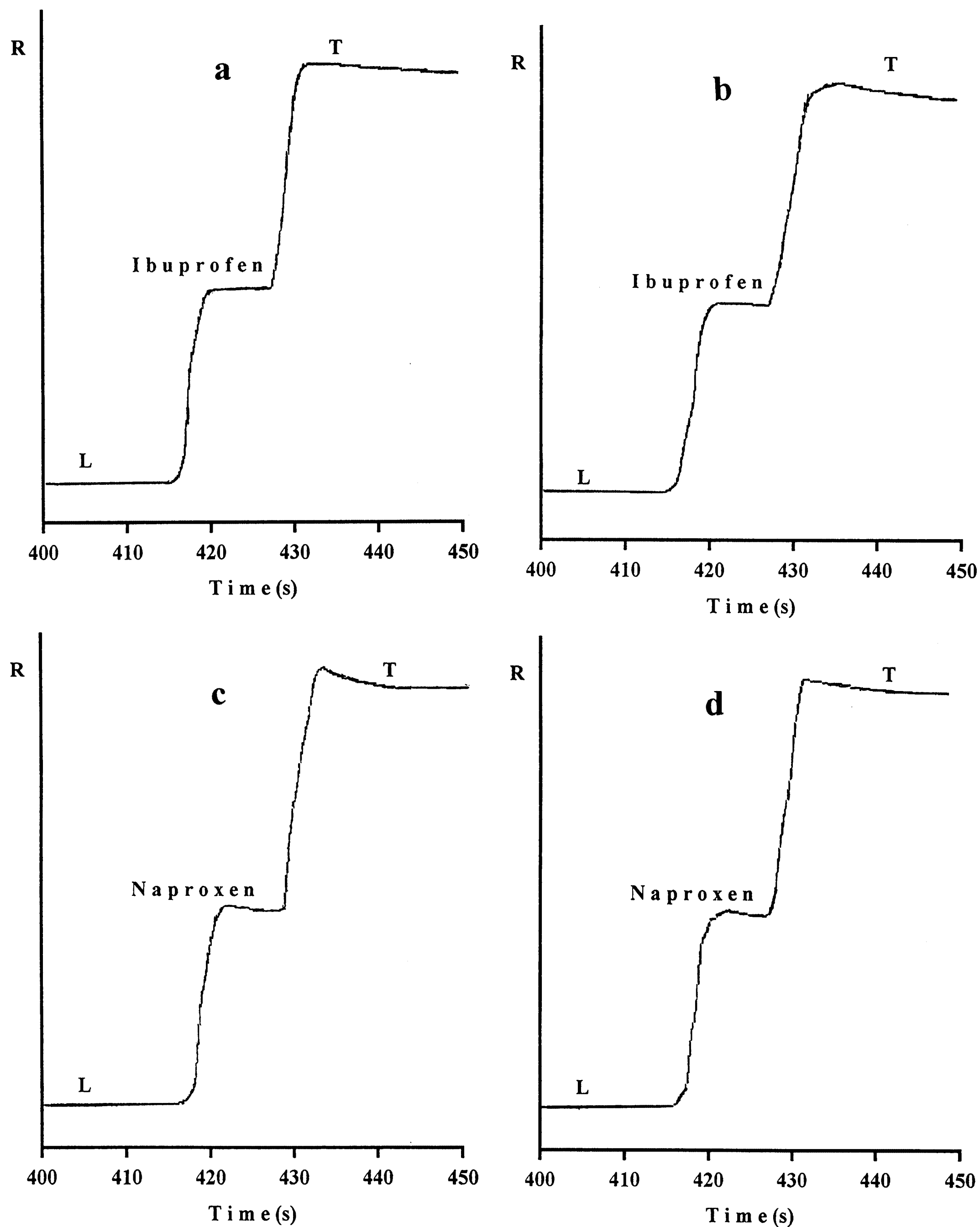

Fig. 1. Isotachopherogram of (a) a standard solution of ibuprofen; (b) a sample solution prepared from the Ibuprofen tablet; (c) a standard solution of naproxen; and (d) a sample solution prepared from the Naprosyn tablet. In all cases, the concentration was 80 mg/l. Leading electrolyte: hydrochloric acid (10 mmol/l) adjusted with creatinine to pH 5.0 plus 0.1% polyvinylpyrrolidone; terminating electrolyte: 10 mmol/l 4-morpholineethanesulfonic acid. L, leading ion; T, terminating ion; R, increasing resistance.

from the Naprosyn tablet. For the Ibuprofen tablet ITP shows only the ibuprofen zone. For the Naprosyn tablet ITP shows only the naproxen zone. No interference from the sample solvent and dosage form excipients could be observed. The fact that the excipients in the above-mentioned tablets do not include acidic substances provides evidence that the excipients do not effect the isotachopherograms. The potential impurities in ibuprofen are: 2-(4-methylphenyl)propionic acid (I); 2-(4-butylphenyl)propionic acid (II); 2-(4-isobutylphenyl)propionamide (III); 2-(3-isobutylphenyl)propionic acid (IV); and 4′-isobutylacetophenone (V) [19]. These compounds were not, however, readily commercially available. Compared with ibuprofen, the first compound (I) has higher effective mobility, while compounds III and V are not acidic compounds. Hence, it is unlikely that interference with ibuprofen would occur in a system such as that described here. Compounds II and IV probably may interfere with the determination of parent drug as similar mobilities to that of ibuprofen could be expected. According to European Pharmacopoeia [20], no naproxen impurities were considered.

In Table 1 the average values and relative standard deviations are given for the relative step heights (RSHs) measured with the conductivity detector. Linearity was observed from 40.0 to 200.0 mg/l of ibuprofen (naproxen), with a coefficient of determination (r^2) of 0.999. The equation for the calibration curve is: $y = a + bx$, where y is the zone length (s) and x is the concentration (mg/l). Calibration data are given in Table 1. For the limit of quantitation (LOQ), the value $(y + 10S)/b$ was used, whereby the calculated intercept of the calibration line can be used as an estimate of y, S is the standard deviation in the y-direction of the calibration line and b is the slope of the calibration line. For the limit of detection (LOD), the value $(y + 3S)/b$ was calculated.

The accuracy and precision of the method were evaluated by analyzing five replicates of spiked samples at each of three concentrations (80.0, 120.0 and 200.0 mg/l) against a calibration curve. The accuracy was given by the percent error [(mean of measured − mean of added)/mean of added] × 100. Precision was evaluated as the relative standard deviation (R.S.D.). The ITP method provides satisfactory precision and accuracy for the analysis of ibuprofen and naproxen (Table 2). The R.S.D. values were found to be between 0.6 and 1.0% for ibuprofen and 0.5 and 1.2% for naproxen. The accuracy was found to be between − 0.7 and − 2.9% for ibuprofen and − 1.4 and + 1.6% for naproxen.

Although all samples in the current study were generally analyzed within 6 h after dissolution, the results of sample stability studies demonstrated that the samples could be stored at 4°C for at

Table 1
ITP and fluorescence results for RSH reproducibility and calibration

Parameter	ITP		Fluorescence spectrometry	
	Ibuprofen	Naproxen	Ibuprofen	Naproxen[a]
RSH	0.44	0.47	–	–
R.S.D. (%) ($n = 5$)	0.9	0.8	–	–
Range (mg/l)	40.0–200.0	40.0–200.0	0.4–2.4	5.0–20.0
Intercept (a)	0.03	0.09	4.4	1.2
Sa[b]	0.08	0.12	7.5	3.2
Slope (b)	0.116	0.109	148.0	11.7
Sb[b]	0.002	0.002	5.2	0.2
r^2[c]	0.9995	0.9995	0.9989	0.9992
LOD/LOQ (mg/l)	2/7	4/12	0.2/0.5	0.9/3

[a] Range (μg/l).
[b] Standard deviation values of intercept (Sa) and slope (Sb).
[c] Coefficient of determination.

Table 2
Determination of ibuprofen and naproxen in synthetic samples

Compound	ITP[a]				Fluorescence spectrometry[b]			
	Added (mg/l)	Found (mg/l)	Accuracy (%)	R.S.D. (%)	Added (mg/l)[c]	Found (mg/l)[c]	Accuracy (%)	R.S.D. (%)
Ibuprofen								
	80.0	79.4	−0.7	0.8	0.80	0.85	+6.2	1.2
	120.0	119.1	−0.7	1.0	1.20	1.18	−1.7	1.2
	200.0	194.2	−2.9	0.6	2.40	2.32	+3.3	1.6
Naproxen								
	80.0	81.3	+1.6	0.5	5.0	4.6	−7.6	2.0
	120.0	118.3	−1.4	0.8	10.0	9.9	−0.5	1.8
	200.0	199.8	−0.1	1.2	20.0	19.4	−3.0	1.6

[a] Based on five replicate analyses.
[b] Based on three replicate analyses.
[c] Concentrations in μg/l for naproxen.

least 5 days without significant degradation. Stored samples were re-analyzed after 5 days and gave acceptable and comparable data to freshly prepared samples. Assay figures were within 3% agreement for stored and freshly prepared samples and no degradation zones were observed in the analysis of the stored sample solutions. Thus, a sample solution shelf-life of 5 days was assigned. A longer shelf-life was not required in this study and therefore a more extensive shelf-life determination was not performed.

For the ruggedness study, preparation of LE and influence of changes of capillaries and instruments were investigated in terms of RSH reproducibility. The ruggedness results are reported in Table 3. As seen in Table 3, LE to LE and instrument to instrument RSH reproducibility falls within the range of normal precision as presented earlier (Table 1). Capillary to capillary reproducibility is somewhat higher.

3.2. Fluorescence spectrometry

Ibuprofen emits maximum fluorescence at 290 nm when excited at 224 nm (Fig. 2). The spectral characteristics are almost independent of the solution pH. No significant changes of the fluorescence intensity as a function of pH were observed. Naproxen solutions show a strong fluorescence which is not dependent over the pH 1–14 range [23]. The excitation and emission spectra of naproxen in phosphate buffer (pH 6.8; 0.04 mol/l) and alkaline aqueous solutions (0.05 mol/l NaOH) are shown in Fig. 3. As seen from Fig. 3, naproxen emits maximum fluorescence at 355 nm when excited at 230 nm. No attempts were made to distinguish between ibuprofen and its possible impurities.

The calibration dependence was polynomial from 0.4 to 6.4 mg/l for ibuprofen and from 5.0 to 30.0 μg/l for naproxen. The calibration plot was found to be linear in the range 0.4–2.4 mg/l for ibuprofen and 5.0–20.0 μg/l for naproxen. The equation for the calibration curve is: $y = a + bx$, where y is the relative fluorescence intensity and x is the concentration of ibuprofen (mg/l) and naproxen (μg/l), respectively. Calibration data are given in Table 1.

Table 3
Reproducibility of ITP method ruggedness

Experimental parameter change	Ibuprofen[a] % R.S.D., RSH	Naproxen[a] % R.S.D., RSH
LE to LE	0.8	0.7
Instrument to instrument	0.9	0.9
Capillary to capillary	1.1	1.0

[a] Sample: 50 μg/ml. Values are the results of five replicate measurements.

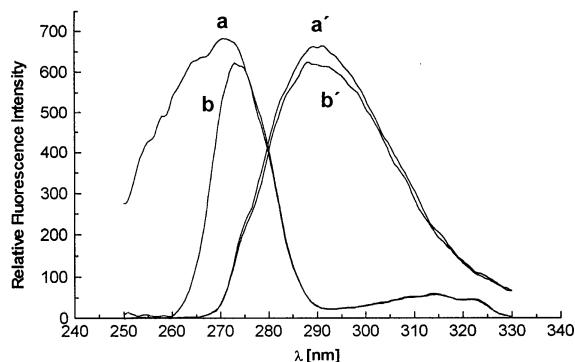

Fig. 2. Fluorescence excitation (a,b) and emission (a′, b′) spectra of ibuprofen in phosphate buffer (pH 6.8; 0.04 mol/l) (a,a′) and 0.05 mol/l NaOH (b,b′). In all cases, the concentration was 4 mg/l. For recording emission spectra λ_{EX}, 224 nm; for excitation, λ_{EM}, 290 nm.

Data for the variation of the precision and accuracy given in Table 2 indicate a R.S.D. from 1.2 to 1.6% and accuracy from −1.7 to 6.2% for ibuprofen and R.S.D. from 1.6 to 2.0% and accuracy from −0.5 to −7.6% for naproxen.

For the ruggedness study, NaOH (0.05 mol/l) preparation to NaOH (0.05 mol/l), and NaOH (0.05 mol/l) to phosphate buffer (0.04 mol/l, pH 6.8), relative fluorescence intensity reproducibility was measured. The ruggedness results are reported in Table 4. As seen in Table 4, NaOH to NaOH relative fluorescence intensity reproducibility falls within the range of normal precision as presented earlier. NaOH to phosphate buffer relative fluorescence intensity reproducibility is somewhat higher.

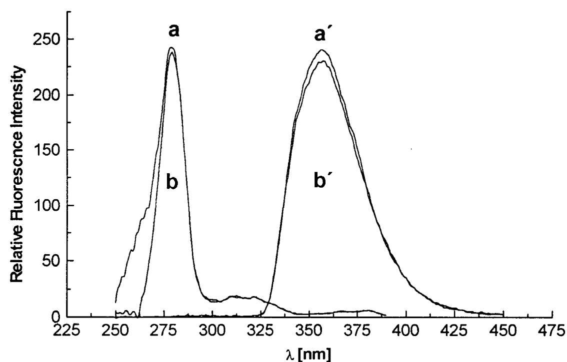

Fig. 3. Fluorescence excitation (a,b) and emission (a′, b′) spectra of naproxen in phosphate buffer (pH 6.8; 0.04 mol/l) (a,a′) and 0.05 mol/l NaOH (b,b′). In all cases, the concentration was 20 μg/l. For recording emission spectra λ_{EX}, 230 nm; for excitation, λ_{EM}, 355 nm.

Table 4
Reproducibility of fluorescence method ruggedness

Experiment parameter change	Ibuprofen[a] % R.S.D., RFI[c]	Naproxen[b] % R.S.D., RFI[c]
NaOH to NaOH	1.4	0.8
NaOH to phosphate buffer	5.6	4.7

[a] Sample: 4 mg/l. Values are the results of five replicate measurements.
[b] Sample: 20 μg/l. Values are the results of five replicate measurements.
[c] RFI, relative fluorescence intensity.

3.3. Stress decomposition studies

To evaluate of the capacity of the ITP method for indicating stability, ibuprofen (naproxen) solutions in NaOH (1 mol/l) and hydrochloric acid (0.1 mol/l) were boiled under reflux for 36 h and analyzed. In the alkaline medium, ibuprofen and naproxen were found undegraded after 36 h, while only 83% (66%) of ibuprofen and 73% (62%) of naproxen were found in the acidic solutions after 24 h (36 h). In both cases, one degradation product appeared just before the primary ibuprofen (naproxen) zone. A high concentration of this product may interfere with determination of the parent drug. If necessary, better separation can be accomplished by reducing the pH of the LE to 4.5–4.0. When naproxen is subjected to acidic hydrolysis by strong acid, it is hydrolyzed to 6-*O*-desmethylnaproxen [23]. As we have shown earlier, naproxen and 6-*O*-desmethylnaproxen could be well separated when the leading electrolyte consisted of 10 mol/l hydrochloric acid, β-alanine, pH 4.0 and 0.1% methylhydroxypropylcellulose [24]. This LE also allowed a better separation of ibuprofen and its degrada-

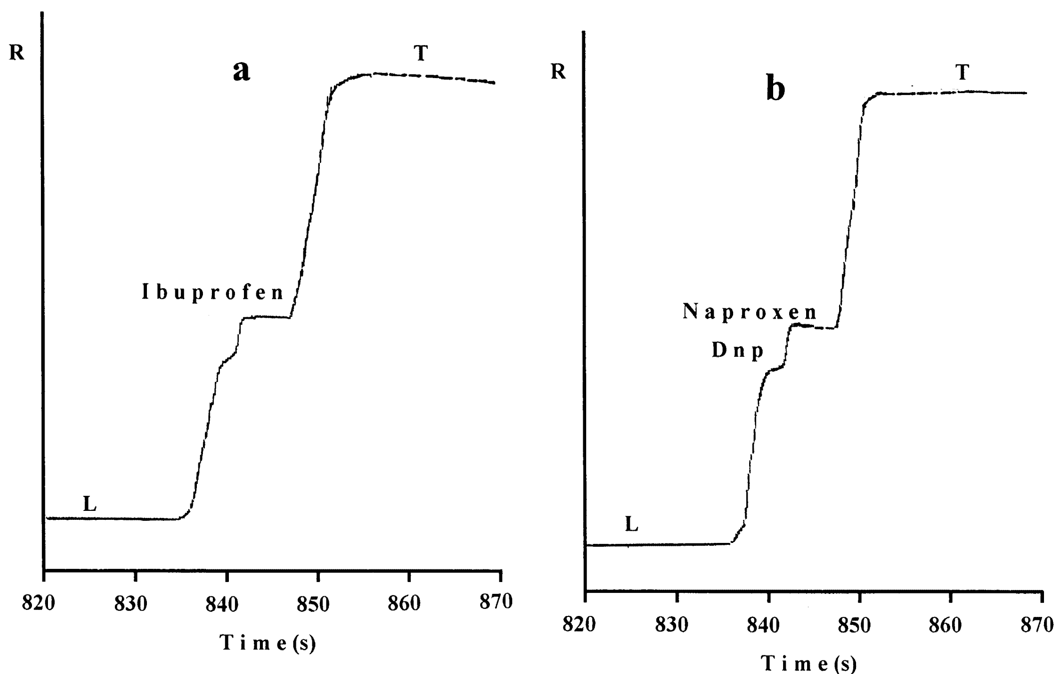

Fig. 4. Isotachopherogram of (a) ibuprofen and (b) naproxen in 0.1 mol/l hydrochloric acid subjected to thermal decomposition for 36 h. Leading electrolyte: hydrochloric acid (10 mmol/l) adjusted with β-alanine to pH 4.0, plus 0.1% methylhydroxypropylcellulose; terminating electrolyte: 10 mmol/l 4-morpholineethanesulfonic acid. Driving current was 250 μA. L, leading ion; T, terminating ion; R, increasing resistance; Dnp, 6-*O*-desmethylnaproxen.

tion product. Fig. 4 shows the isotachopherograms of ibuprofen and naproxen in 0.1 mol/l hydrochloric acid subjected to thermal decomposition for 36 h. The fluorescence method shows comparable values for the undegraded amounts of ibuprofen and naproxen. In the alkaline medium, ibuprofen and naproxen were found undegraded after 36 h, while only 79% (65%) of ibuprofen and 75% (63%) of naproxen were left in the acidic solutions after 24 h (36 h). In the case of ibuprofen, no degradation product appeared in the emission spectra (Fig. 5). For naproxen in acidic medium, the emission bands of naproxen (λ_{EM} = 355 nm) and 6-*O*-desmethylnaproxen (λ_{EM} = 420 nm) were quite satisfactory resolved so as to be useful for the direct simultaneous determination of both compounds (Fig. 6). However, spectral overlaps may occur in their binary mixtures when one compound is present in large excess. For separating binary mixtures of naproxen and 6-*O*-desmethylnaproxen the synchronous scanning approach was used [23,24].

3.4. Determination of ibuprofen and naproxen

The ITP and fluorescence methods were then applied for the determination of ibuprofen and naproxen in tablets; the results are given in Table 5. As can be seen, the two techniques seem to be

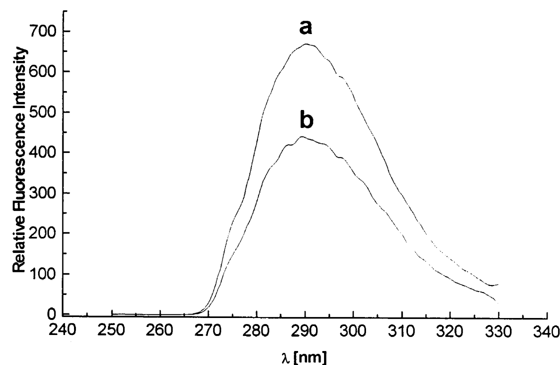

Fig. 5. Fluorescence emission spectra of ibuprofen in 1 mol/l NaOH (a) and 0.1 mol/l hydrochloric acid (b) subjected to thermal decomposition for 36 h. λ_{EX}, 224 nm.

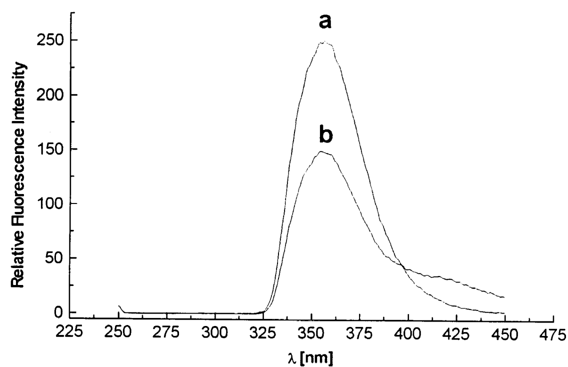

Fig. 6. Fluorescence emission spectra of naproxen in 1 mol/l NaOH (a) and 0.1 mol/l hydrochloric acid (b) subjected to thermal decomposition for 36 h. λ_{EX}, 230 nm.

suitable to carry out the determination of the ibuprofen and naproxen in the usual concentrations that they are found in the analyzed samples, that is, considering the original quantities in the tablets. The best LOQ was obtained by using fluorescence spectrometry. Considering that the obtained LOQ values are in any case much smaller than the concentration values expected to be observed from real samples, it can be concluded that the two techniques are suitable to carry out this type of determination. From the values given in Table 5 it can be deduced that ITP and fluorescence spectrometry render similar repeatability for ibuprofen, while ITP gives better results in terms of repeatability values of naproxen. The influence of the matrix can be responsible of the poor repeatability values obtained with fluorescence spectrometry.

To compare the performances of HPLC, CE and ITP, the within-day precision for corrected migration time, RSH, peak area and zone length were considered and the calibration graphs obtained using the different methods were compared (Table 6). In the analyses with HPLC, CE and ITP for both components, a linear relationship between measured peak area or zone length and concentration of the components is obtained with r^2 better than approximately 0.999. Concentration sensitivity of ITP is comparable with that of CE, although the mass sensitivity of CE is higher than that of ITP. The reason is that the injection volume in CE lies in the range of several nanoliters while that in ITP is in the range of microliters. The concentration sensitivity of CE is generally lower than that of HPLC when UV absorbance detection is employed in both techniques. This is due to the to short path length imposed by the small diameter in CE. The within day-precision with the CE method for corrected migration times was less than 1%; the ITP method has the same order of within-day precision of the RSHs. Precision of injection, as measured in peak area repeatability is generally poorer in CE than in HPLC, typical values being 1–2% and 0.5–1%

Table 5
Analysis of dosage forms

Product (active compound)	Label claim (mg)	ITP Assay result (mg)	ITP Recovery (%)	ITP R.S.D. (%)	Fluorescence spectrometry Assay result (mg)	Fluorescence spectrometry Recovery (%)	Fluorescence spectrometry R.S.D. (%)
Ibuprofen	200	203.0	101.5	1.2	199.3	99.6	2.1
(ibuprofen)	200	192.4	96.2	1.8	196.1	98.0	1.3
	200	196.8	98.4	1.4	195.8	97.9	1.8
	200	201.7	100.8	0.9	200.0	100.0	3.1
	200	203.0	101.5	1.5	201.3	100.6	1.2
	400	399.9	100.0	1.9	399.4	99.8	1.8
Naprosyn	250	252.0	100.8	2.0	251.2	100.5	4.5
(naproxen)	250	252.0	100.8	1.2	254.7	101.9	3.6
	250	254.0	101.6	1.3	249.4	99.8	3.6
	250	249.4	99.8	1.3	250.6	100.2	5.5
	250	248.3	99.9	2.1	245.0	98.0	3.6

Table 6
Validation data of the HPLC, CE and ITP methods

Parameter	Ibuprofen				Naproxen		
	HPLC [6]	HPLC [5]	CE [15]	ITP	HPLC [6]	CE [18][a]	ITP
% R.S.D., RSH[b]				0.9		0.8–0.9[b,c]	0.8
Linearity range tested (μg/ml)	0–60	2–10	5–50	40–200	0–60	40–120 (1.4–28)	40–200
r^2	0.9994		0.9996	0.9995	0.9995	0.9994 (0.9957)	0.9995
LOD	0.5 ng	50 ng/ml	1μg/ml	2 μg/ml	0.5 ng	(210 ng/ml)	4 μg/ml
% R.S.D., peak area	0.2	0.8	0.4–1.3	1–2 (zone length)	0.2	0.7–1.7 (1.9–9.0)	1.2–2 (zone length)
Run time (min)	11	12.5	7	7	8	9	7
Detection	UV 225 nm	UV 215 nm	UV 214 nm	Conductivity	UV 260 nm	UV 210 nm	Conductivity

[a] Data for *S*-naproxen. Data for *R*-naproxen are in the brackets.
[b] Corrected migration time for CE.
[c] Data from [17].

R.S.D., respectively. The within-day precision with the ITP method for the zone lengths was 1–2%. It can be concluded that the precision of HPLC experiments is by far the best. The sample preparation method employed for ITP is similar to that for CE and HPLC. The assay time by ITP and CE is shorter than that by HPLC. A long preconditioning process is required only for HPLC. Flushing with NaOH solution and buffer or LE is sufficient in CE and ITP. ITP offers same advantages over conventional chromatographic methods: (i) non-ionic compounds, which are frequently components of the tablets, do not interfere with the analysis of the ionic compounds; (ii) low running cost (two order of magnitude compared with HPLC), decreased cost of capillaries; and (iii) no organic solvents are used in the preparation of LE. The largest drawback of ITP is lower resolution as compared with CE.

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