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Determination of nabumetone in pharmaceutical formulation by flow injection analysis (FIA) with UV-detection

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A precise and accurate FIA method for the quantification of nabumetone (NAB) in pharmaceuticals is described. The best suitable carrier solvent system consisted of ethanol : water (30 : 70 v/v). Sample solution (4.7×10^{-6} M NAB) was prepared in this solvent and injected to the instrumental system at a flow rate of 1.2 ml · min^{-1}. The signals were detected by a UV detector at 228.8 nm. The calibration curves of NAB was linear in the concentration range of 1.4×10^{-6} M–2.8×10^{-5} M. The intra- and inter-assay precision were less than 2.6%. The method exhibited a good linearity with the correlation coefficients. The LOD and LOQ values were found to be 4.4×10^{-7} and 1.3×10^{-6} M, respectively. The effects of the tablet excipients were insignificant at the 95% probability level. The calculated tablet content was 99% which is agreement with the ranges stated by pharmacopoeias.

1. Introduction

Nabumetone [NAB] 4-(6-methoxy-2-naphthalenyl)-2-butanone is a naphthylalkanone structured non-steroidal anti-inflammatory drug (NSAID). It has an analgesic and anti-inflammatory effects in the treatment of rheumatoid [1] and osteoarthritis [2].

NAB is well absorbed from the gastrointestinal system [3] and converted to an active metabolite after extensive first-pass metabolism 6-methoxy-2-naphthylacetic acid (6-MNA) [4]. 6-MNA, a selective cyclooxygenase-2 inhibitor, is subsequently conjugated and excreted in urine with an elimination half-life of 20–24 h [5].

A limited number of different analytical techniques have been used for the determination of NAB in drug products and biological samples. In these studies NAB concentrations were generally determined by HPLC using UV and fluorimetric detection [6–9]. The proposed method in the British pharmacopoeia (BP 1998) [10] is also a liquid chromatographic method with UV detection. No flow injection analysis method has been reported so far for the determination of NAB in pharmaceutical tablets.

The aim of this study is to develop a new analytical method for simple, sensitive and rapid determination of NAB in pharmaceutical tablets.

2. Investigations, results and discussion

The appropriate carrier solvent which is suitable to dissolve NAB was found to be 30% ethanol and it was used throughout the study. This solvent did not cause any precipitation of NAB.

For optimization of the instrumental conditions, initial spectrophotometric studies were carried out using a solution of NAB (4.7×10^{-5} M). A peak with an intensive absorbance appeared at 228.8 nm and absorbance versus concentration was linear in the range of 1.4×10^{-6}–2.8×10^{-5} M. A very good calibration relation was obtained that fits to the equation [$A = 8134.8\ C_x(M) + 0.0110$; $r = 0.9997$].

For the examination of FIA conditions, the effect of flow-rate was investigated by pumping the carrier solvent in the range of 0.1–3.0 ml · min^{-1}. The relation of signals as area depending on the flow-rate exhibited a parabolic curve. Linearity dependence was provided by a function of $y = f(1/x)$ where the equation fit to [$y = 3.1 \times 10^{-6}x - 2.3 \times 10^{-8}$; $r = 0.9991$]. Although, the flow-rate values are equivalently useable for this system, a flow rate of 1.2 ml · min^{-1} was employed for the rest of the study.

The repeatability of the method was tested by applying eight injections for three consecutive days. The inter-day precision was performed by applying the intra-day injections of three different days.

The results and the statistical data calculated from the intra- and inter-day injections of 4.7×10^{-6} M NAB are shown in Table 1.

Table 1: Intra- and inter-day repeatability of the method

Parameters	Intra-day precision			Inter-day precision
	First day (n = 8)	Second day (n = 8)	Third day (n = 8)	(k = 3; n = 24)
Mean	270951	273650	278800	274467
SD	5194	5345	7110	6585
RSD (%)	1.9	2.0	2.6	2.4
CL 0.05	3599	3704	4927	2358

Table 2: Linearity of NAB in the range of 1.4×10^{-6} M and 4.7×10^{-5} M

Parameters	Intra-day			Inter-day
	First day (n = 5)	Second day (n = 5)	Third day (n = 5)	Whole days (k = 3; n = 15)
Slope, a	4.381×10^{10}	4.439×10^{10}	4.239×10^{10}	4.353×10^{10}
Intercept, b	9431	5643	15490	10190
Correlation coefficient, r	0.9999	0.9997	0.9996	0.9998
SD of regression equation, ±Sr	1.998×10^{3}	3.897×10^{3}	4.110×10^{3}	9.026×10^{3}
SD of the Slope, Se	5.329×10^{8}	1.039×10^{9}	1.096×10^{9}	1.390×10^{9}
CL (p = 0.05)	$\pm 5.076 \times 10^{8}$	$\pm 9.901 \times 10^{8}$	$\pm 1.0443 \times 10^{8}$	$\pm 6.3168 \times 10^{8}$

The RSD values were found to be lower than 2.6 for intra and inter-day examinations indicating that the method is significantly precise.

The linearity of the method was examined in the range of 1.4×10^{-6} M and 4.7×10^{-5} M according to the intra- and inter-day statistical analysis of the calibration sets and their responses. It deviates at around 2.8×10^{-5} M. The linearity and the accuracy of the method are shown in Table 2.

Satisfactory results were obtained for linearity which leads us to conclude that the method is reliable for the quantification of NAB.

The limit of detection (LOD) (S/N = 3.3) and the limit of quantification (LOQ) (S/N = 10) values were 4.4×10^{-7} and 1.3×10^{-6}, respectively. These values are in agreement to methods reported elsewhere [7–9].

A synthetic placebo tablet powder was prepared consisting the most conventional components of the pharmaceutical tablet formulations to examine the effect of the excipients on the determination of NAB. Approximately, 25 mg placebo tablet powder weighed in 15 different tubes (l = 3; n = 5) and with the addition of 1 ml of 4.7×10^{-4} M NAB solution the mixture was shaken for 5 min and after 1 h incubation it was centrifuged at 4000 rpm for 10 min. The solutions made up to 10 ml with 30% ethanol, re-centrifuged and diluted 10 times to the concentration level of 10^{-5} M. The final analysis solutions were prepared using these solutions at the concentrations of 2.3×10^{-6} for 50%, 4.7×10^{-6} for 100% and 7.0×10^{-6} for 150% of a tablet. Furthermore, the same dilutions without placebo were prepared to find out their recovery. The mean, standard deviation, relative standard deviation and the 95% confidence interval of the method from the results were calculated and shown in Table 3.

Table 3: Intermediate precision of NAB which corresponds to the values at 50, 100 and 150 percent of a tablet performed under optimum conditions

	50% (n = 5)	100% (n = 5)	150% (n = 5)
Mean	99.4	99.5	99.1
SD	1.76	1.74	1.90
RSD	1.77	1.75	1.92
CL (p = 0.05)	1.54	1.52	1.66

Table 4: Assay of Relifex® 500 mg tablets

Mean (mg)	499.4
Standard deviation (SD)	0.50
Relative Standard deviation (% RSD)	0.50
Confidence limit (CL) 0.05 (mg)	499.4 ± 0.44

Carrier solvent 30% ethanol, flow-rate 1.2 ml · min^{-1}, detection at 228.8 nm, injection volume 20 µl at room temperature (n = 6)

The adsorption or probable interaction that could affect the determination of NAB was not observed for three groups. Recovery was higher than 99%, therefore it is concluded that the excipients do not interfere with the proposed method.

The determination of NAB tablets was performed at optimum conditions as discribed in the experimental section. Six different experiments were performed and the content of Relifex® 500 mg tablets was determined. The results are shown in Table 4.

The proposed method for the determination of NAB in tablets and solutions is rapid, accurate and sensitive. The total analysis time of the proposed FIA method is less than the standard HPLC techniques for tablets [6–9]. The composition of the carrier solvent system makes the method cost effective and simple if compared to the HPLC method. The active material content of nabumetone in Relifex® 500 mg tablet was found to be 499.4 ± 0.44 mg which is in agreement with the official pharmacopoeia specifications (BP 1998) [10].

In conclusion, the proposed FIA method is reliable, precise, accurate, simple and fast which makes it suitable for routine analysis of NAB pharmaceutical table formulation.

3. Experimental

3.1. Chemicals

Standard NAB was obtained from Glaxo-Smith Kline İlaç San (Istanbul, Turkey). All the other chemicals were HPLC gradient grade and supplied from Merck Co, (Darmstadt, Germany). Double distilled water was used throughout this study. The pharmaceutical form of NAB used was Relifen® 500 mg tablet produced by Fako İlaçlari AŞ, (Istanbul, Turkey).

3.2. Apparatus

A model of LC-6A Liquid Chromatograph pump with a 20 µl loop was used for the separation of compound signals which were detected by a model of SPD-10A UV-VIS detector. The results were processed by a model of C-R7A Chromatopac integrator. The carrier solvent 30% ethanol was delivered with the plunger pump at a flow rate of 1.2 ml · min^{-1}. The solutions were injected (20 µl) manually and the absorbance was measured at 228.8 nm.

3.3. Procedures

3.3.1. Standard solutions

Standard stock solutions of NAB (4.7×10^{-4} M) prepared by dissolving appropriate amounts of NAB in 30% ethanol at room temperature. Since NAB is highly non-polar, it was dissolved in ethanol and then the dilutions were prepared in a way that the final solvent strength was 30%. Solutions were stored in a refrigerator and protected from light.

3.3.2. Analysis of tablets

For the quantification of NAB in tablets, ten NAB tablets were accurately weighed. The average weight of a tablet was calculated (0.638 mg) and the tablets were powdered and mixed finely in a mortar. A sufficient amount of tablet powder equivalent to the weight of one tablet was accurately weighed and transferred to a 100 ml volumetric flask. After addition of 30 ml of ethanol, the volume made up to 100 ml with double distilled water and the solution was magnetically stirred for 10 min. The solution was transferred to tubes and centrifuged at 4000 rpm for 10 min. The supernatant of the solution was injected to the instrumental system and peak area values were calculated.

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