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Simplex optimization and kinetic determination of nabumetone in pharmaceutical preparations by micellar—stabilized room temperature phosphorescence

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Abstract

The present method described the kinetic determination of nabumetone, a non-steroidal anti-inflammatory drug, by means of micellar-stabilized room temperature phosphorescence (MS-RTP), using the stopped-flow mixing technique. This methodology enables us to determine analytes in complex matrices without the need for a tedious separation process, as well as greatly diminishes the time for the analysis.

Firstly, chemical and instrumental variables affecting the rate of phosphorescent development and the intensity of the signal, were found using a simplex optimization procedure. As application, nabumetone was determined in commercial Spanish pharmaceutical preparations.

With the proposed method, the maximum signal of phosphorescence appears in only 10 s once the sample has been prepared, and the maximum slope of the kinetic curve, corresponding with the maximum rate of the phosphorescence development, was measured at λ_{ex} = 271 nm and λ_{em} = 520 nm. The overall least-squares regression to find the straight line that fitted the experimental data, the detection limit, the repeatability and the standard deviation for replicate sample, were also determined.

The proposed method was validated versus a HPLC method with satisfactoty results.

Keywords: Nabumetone; Room temperature phosphorescence; Simplex; Stopped-flow; Kinetics

1. Introduction

Nabumetone (4-(6-methoxy-2-naphthyl)butan-2-one), whose structure is shown in Fig. 1, is a non-steroidal anti-inflammatory drug (NSAID) from the 2,6-disubstituted naphthyl-alkanones class. Nabumetone is metabolized to an active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA), which is excreted in urine. Both, drug and metabolite, bind extensively to albumin plasma [1].

Nabumetone, a commercially available drug, is reported as being less aggressive as far as secondary effects are concerned while, at the same time being relatively efficient as an anti-inflammatory drug with analgesic properties [2–4].

There are some reports of spectrophotometric and chromatographic analytical procedures for the assay of nabumetone and its main metabolite. Thus, several authors proposed methods for the determination of nabumetone in pharmaceutical preparations by measuring its absorbance directly [5–6] or after a derivation process to form colourful compounds [7]. Recently, the determination of nabumetone in pharmaceutical preparations using flow injection analysis with UV detection has been described obtaining satisfactory results without interference from its excepients [8].

Nevertheless, nabumetone has been mainly determined by reversed-phase high-performance liquid-chromatographic and UV detection [9–11].

Escuder-Gilabert et al. [12] proposed the determination of some non-steroidal anti-inflammatory drugs, including nabumetone, in pharmaceutical preparations using a liquid-chromatographic procedure. The compounds were separated

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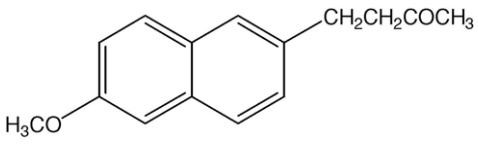

Fig. 1. Structure of nabumetone.

on a C18 Kromasil analytical column; the mobile phase was 0.06 M cetyltrimethylammonium bromide, at pH 7, containing 10% of 1-butanol. Recoveries were between 95% and 108% of the nominal content and relative standard deviations were <6%.

Nabumetone has been also quantificated in pharmaceutical preparations using a gas-chromatographic procedure [13] on a glass column of Shimalite operated at 215 degree with nitrogen as carrier gas and a flame ionization detector. Recovery was 99.9% and the coefficient of variation was 0.27%.

Recently, an isocratic reversed-phase liquid-chromatographic method was developed for simultaneous determination of naproxen, nabumetone and its major metabolite, 6-methoxy-2-naphthylacetic acid, in pharmaceutical preparations and human urine [14].

The method described in this paper is based on obtaining a phosphorescence signal from this anti-inflammatory drug using sodium dodecyl sulfate (SDS) as micellar agent, thallium(I) nitrate ($TlNO_3$) as heavy atom and sodium sulfite (Na_2SO_3) as deoxygenator agent. This technique, named micelle-stabilized room temperature phosphorescence (MS-RTP), has been used in combination with the stopped-flow mixing technique. This combination is especially useful when the phosphorescent signal is unstable or takes a long time to stabilize as the use of stopped-flow avoids the delay involved in bath techniques, because the fast through mixing of the streams from the syringes in the flow cell, resulting from the pressure exerted by the instrumental system, favors the interaction of oxygen molecules with sulfite ions and their removal, which hinders application of a phosphorescence method to routine analyses. This approach can be used to develop kinetic determination methods by measuring the slope of the kinetic curve obtained, which are directly proportional to the analyte concentration. Panadero et al. reported for the first time this procedure for the determination of carbaryl in water [15] and naproxen in serum [16]. This approach has later been applied to the determination of other phosphorescent species by Murillo et al. [17-19] in a similar way as that described in the first article.

The various dependent chemical and instrumental conditions affecting the phosphorescence signal of nabumetone, were determined following a simplex as a method for the direct search of the optimum of a function.

In the original simplex method (SM) described by Spendley et al. [20], the procedure begins by the choice of three $k + 1$ points, being K the number of dependent variables, and the evaluation of the response at each and the continual formation of new simplexes by reflection of the remaining points. Nelder and Mead [21] described a new method in which the simplex adapts itself to the local of space, elongating down long inclined planes, changing direction on encountering a valley at an angle, and contracting in the neighborhood of a minimum; this method is referred to as the modified simplex method (MSM). Furthermore, there exists a new nonlineal optimization technique based on the MSM; this new technique has been described by Ryan et al. [22] and shows promise as a method for accurately finding the region of an optimum. With the combination of the MSM and the nonlineal optimization technique it is not necessary to begin and continue the simplex with an equilateral geometrical figure, as we do in the method proposed, in order to achieve, in a fast and easy way, the optimum value of the dependent variables involved in MS-RTP.

2. Experimental

2.1. Instruments

The phosphorimetric measurements were performed on an Aminco Bowman Series 2 luminescence spectrometer, connected to a PC microcomputer with the AB2 software, which runs on the Windows'98 operating system. The instrument utilizes a 7 W integral pulsed xenon lamp for phosphorescence measurements. To measure the kinetic luminescence reactions, the instrument incorporates the MilliFlow stopped-flow reactor, allowing the study of changes in luminescence reactions when two reactants are vigorously forced through the mixing chamber and suddenly stopped in the observation cell.

The MilliFlow stopped-flow reactor consists of two fill syringes, two drive syringes, an observation cell (path length of 2 mm), a stop syringe, a stop block, an exhaust, and fill valve levers. Hamilton gasting syringes of 2.5 mL (drive syringes) were used to contain the two reactant solutions. The syringes are made from controlled inner diameter, borosilicate glass with precision-machined Teflon plunger tips (these pistons are simultaneously driven by an air-operated plunger). Thermostatic equipment allows maintenance of a constant temperature of 20 °C into the MilliFlow stopped-flow reactor.

A Crison model 2001 pH-meter with a glass-saturated calomel combination electrode was used to measure pH of solutions.

2.2. Software

The AB2 program allows file management, defines parameters of the instrument for the acquisition, and sets up the acquisition parameters to obtain excitation and emission spectra and kinetic curves.

The kinetic curve processing was performed by means of the SLOPES program developed by us, which calculates the linear region optimization in the kinetic curve and fits data