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Simple determination of propranolol in pharmaceutical preparations by heavy atom induced room temperature phosphorescence

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Abstract

The applicability of heavy atom induced room temperature phosphorescence in real samples is demonstrated in this work. In this methodology only two reagents, potassium iodide as heavy atom salt and sodium sulphite as oxygen scavenger, were used to obtain phosphorescent signal of propranolol in solution. Thus a new simple, rapid and selective phosphorimetric method is proposed for propranolol determination in pharmaceutical preparations. The phosphorescence intensity was measured at 492 nm exciting at 294 nm. Phosphorescence was fully developed instantly, obtaining a linear concentration range between 0 and 500 ng ml^{-1} with a detection limit of 14.4 ng ml^{-1}, an analytical sensitivity of 6.7 ng ml^{-1} and a standard deviation of 1.4% at a 300 ng ml^{-1} concentration level. The method has been successfully applied to the analysis of propranolol in an antidepressive pharmaceutical preparation and it was validated using standard addition methodology.

Keywords: Pharmaceutical analysis; Propranolol; Heavy atom induced (HAI); Room temperature phosphorescence (RTP)

1. Introduction

Propranolol has a specific blocking action on the adrenergic beta-receptors and inhibits the sympathetic stimulation of the heart. It is used in the treatment of cardiac arrhythmias associated with heart disease, digitalis intoxication, hypertension, etc. For this reason, it is necessary to develop highly selective and facile procedures for the determination of propranolol in pharmaceutical preparations.

Several analytical procedures for propranolol analysis in different matrices have been described [1–5]. Among the optical techniques, quite a big number of spectrophotometric [6–8] and fluorimetric methods [9–11] are described, however, only a few phosphorimetric methods for propranolol determination have been proposed even though the selectivity attained in phosphorimetry

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is much larger than that expected in spectrophotometry or fluorimetry.

The phosphorimetric methods in solid support offer the advantages of wide linear dynamic ranges [12,13] but its use in flow systems is limited. On the other hand, the micelle and cyclodextrin-stabilized phosphorimetric methodologies in solution presents stabilization times of 30 min [14,15].

Recent studies have demonstrated that the RTP emission of naphtalene derivatives can be directly induced in aqueous solutions only by the addition of high concentrations of an heavy atom perturber and sodium sulphite as a chemical deoxygenator [16–24].

This methodology named Heavy atom induced room temperature phosphorescence (HAI-RTP), have been applied to determine different interesting substances as naphazoline, naproxen and nafronyl in pharmaceutical preparations [16–18] and some pesticides in vegetables matrices [19–21]. This phenomenon has been confirmed by Li et al. in several simultaneous publications [23,24].

In this work a simple, selective and faster phosphorimetric method, based in obtaining phosphorescent signals in solution without using organised media, is proposed for propranolol determination.

2. Experimental

2.1. Instrumentation

All recordings of uncorrected luminescence spectra and measurements of relative phosphorescence intensity (RPI) were carried out with an Aminco Bowman Series 2 luminescence spectrometer equipped with a 7 W pulsed xenon lamp and a thermostated cell holder. The system was controlled with a personal computer with 4 MB RAM memory, OS/2 version 2.0, and a GPIB (IEEE-488) interface card for computer-instrument communication.

2.2. Reagent and solutions

Analytical reagent-grade chemicals were employed for the preparation of all the solutions. Thallium(I) nitrate, potassium iodide, potassium bromide, potassium chloride, sodium iodide, sodium bromide, sodium chloride and anhydrous sodium sulphite were purchased from Sigma and were used as received. A total of 2 M solutions for most heavy atom salts were prepared. Thallium nitrate solution at a 0.25 M concentration was prepared. The 0.1 M sodium sulphite solutions were prepared daily and kept in tightly stoppered containers.

Aqueous solutions (25 μg ml^{-1}) were prepared for propranolol (Sigma Chemical Co.). The water used was twice distilled and prepared with a Milli-Q system (Millipore, Bedford, MA).

2.3. General procedure

A 40 μl aliquot of propranolol stock solution with a 9 ml of 2 M potassium iodide and 400 μl of 0.1 M sodium sulphite were introduced into a 10 ml calibrated flask and made up to volume with water. Standard 10 mm quartz cells were used in all cases.

The phosphorescence intensities of the samples and the corresponding blanks were measured at the phosphorescence wavelength maxima of $\lambda_{ex}/\lambda_{em}$ 294/492 nm, $slits_{exc/em}$ 16/16 nm, decay time and gate time 250 and 250 μs respectively and detector voltage 1000 V.

2.4. Sample preparation

The proposed method has been applied to the analysis of propranolol in a commercial pharmaceutical preparation called Sumial 10 (Zeneca Farma S.A., Spain). The nominal content per tablet is 10 mg of hydrochloride propranolol accompanied by excipients without indications of their concentration. The contents of ten tablets were mixed and taken for analysis and the solid was powdered and homogenised. A portion was dissolved in doubly distilled water and several aliquots of this solution were treated as indicated under general procedure.

3. Results and discussion

3.1. Phosphorescence properties

Fig. 1 shows the excitation and phosphorescence emission spectra of propranolol in aqueous solution. Propranolol emits phosphorescence with a maximum excitation intensity at 294 nm and two maximum emission intensities at 492 and 526 nm. The best signal/noise relation was obtained at the wavelength emission of 492 nm. In the experimental conditions, the half life time of the propranolol phosphorescence emission is 1290 μs.

Different instrumental parameters related to the luminescence technique affect the phosphorescence response, so they were carefully selected (see Table 1). All these optimal instrumental parameters were kept constant for the rest of the experimental work.

3.2. Influence of heavy atom perturbers

Different heavy atoms salts (KI, NaI, KBr, NaBr, KCl, NaCl and $TlNO_3$) were studied as heavy atom perturbers to observe the HAI-RTP emission of the propranolol. Only KI and $TlNO_3$ permit to observe phosphorescence signal of propranolol by HAI-RTP being the most intense the one obtained using KI.

No-phosphorescence response of propranolol is obtained in the total absence of KI while a marked increase in the phosphorescence signal with an increase in the heavy atom concentration was observed. As a result of these studies, the optimum concentration of KI selected to observe propranolol phosphorescence emission was 3.6 M (see Fig. 2).

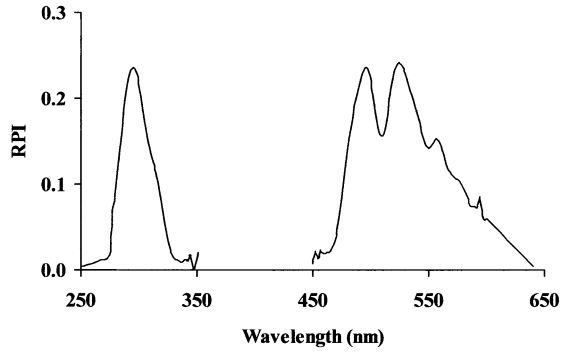

Fig. 1. Projected two-dimensional spectrum of propranolol. [Propranolol] = 100 ng ml^{-1}, [KI] = 3.6 M, [Na_2SO_3] = 0.005 M. Excitation and emission wavelengths 250–350 nm and 450–650 nm respectively, $slits_{exc/em}$ 16/16 nm, $t_{d/g}$ 250/250 μs and detector voltage 1000 V.

Table 1
Optimum instrumental parameters

Instrumental parameters	Optimum values
Wavelength (excitation/emission)	294/492 nm
Delay time (t_d)	250 μs
Gate time (t_g)	250 μs
Slits (excitation/emission)	16/16 nm
Detector voltage	1000 V

3.3. Influence of deoxygenation and pH

In this work, sodium sulphite was selected as deoxygenation scavenger. Although in aqueous solution the elimination of dissolved oxygen is practically immediate, both the relative phosphorescence intensity and the stabilization time (necessary time to sample deoxygenation) variations with concentration of sodium sulphite have been studied. This was performed by monitoring the signal as a function of time until the HAI-RTP signal was stabilised for at least 2 min. To find the optimum concentration of sodium sulphite, different amounts between 1.0 and 8.0 mM were added to a solution with a fixed concentration of

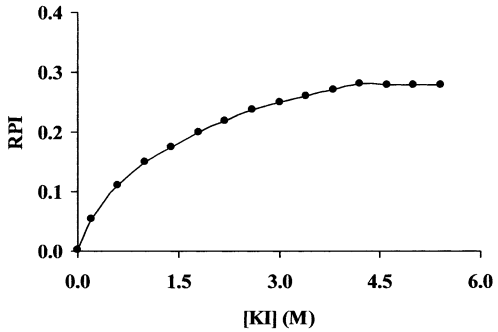

Fig. 2. Influence of heavy atom salt concentration on the HAI-RTP of propranolol. [Propranolol] = 100 ng ml^{-1}, [Na_2SO_3] = 0.005 M. $\lambda_{exc}/\lambda_{em}$ 292/524 nm, $slits_{exc/em}$ 16/16 nm, $t_{d/g}$ 250/250 μs and detector voltage 1000 V.

propranolol in the presence of the heavy atom salt selected. A 5.0 mM sodium sulphite solution was selected as optimal (see Fig. 3).

Various pHs, from 4 to nearly 10, were tested with a solution containing a fixed amount of propranolol, heavy atom salt and sulphite. With pHs greater than 6.5 the HAI-RTP signal was constant and the stabilisation time was practically instantaneous. In these optimised experimental conditions it was observed that the system has a pH of 8.5, so the use of a buffer solution is not necessary.

3.4. Effect of organic solvents on HAI-RTP intensity

The mayor limitation of HAI-RTP is the impossibility of working with water-insoluble substances. The effect of different percentages of five organic solvents miscible with water (ethanol, methanol, acetonitrile, dimethylformamide and acetone) were studied in order to improve the propranolol solubility.

The study carried out demonstrated that no changes in relative phosphorescence intensity using ethanol, methanol and dimethylformamide up to 5% was observed. However, the presence of 1% of acetone or/and acetonitrile produce an important phosphorescence quenching of the phosphorescence signal. With respect to the stabilisation time, an increase was observed in all cases except for ethanol.

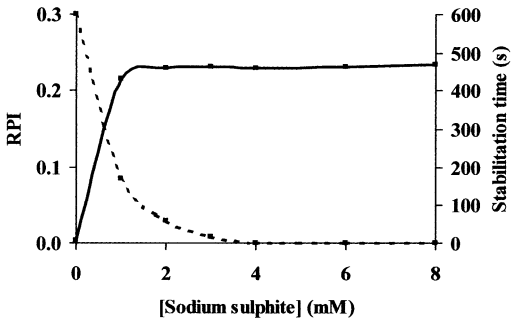

Fig. 3. Influence of sodium sulphite concentration on the HAI-RTP of propranolol. [Propranolol] = 100 ng ml^{-1} and [KI] = 3.6 M. The instrumental parameters as Fig. 2.

3.5. Effect of temperature and stability

The temperature affects both oxidation rate of sulphite by the oxygen present in the solutions and the intensity of the phosphorescence signals. High temperatures accelerate the rate of oxidation of sulphite by oxygen and decreases the phosphorescence intensities observed. We have carried out a detailed study of the effect of temperature on the HAI-RTP emission in the range 5–50 °C. This study confirms that the RTP intensity decreases almost linearly as the temperature is increased. A temperature of 25 °C was chosen to facilitate the experimental work. Under these experimental conditions, phosphorescence signals for the propranolol were obtained instantaneously and remain stable for at least 1 h.

3.6. Calibrations, sensitivity and precision

Analytical performance characteristics of the proposed method were evaluated. Standard calibration graph was prepared according to recommended procedure for the propranolol. The wide linear range, small standard errors and correlation coefficient indicate very good calibration linearity. The detection and quantification limit, sensitivity and precision, expressed as relative standard deviation, was determined using the method proposed by Cuadros et al. [25]. Three replicates for the propranolol solution of 0, 100, 200, 300, 400 and 500 ng ml^{-1} were taken in order to set up the calibration. All the features of the proposed method are summarised in Table 2.

3.7. Analytical applications

The low detection limits and the good analytical sensitivity of the proposed method makes possible the determination of propranolol in pharmaceutical preparations. The proposed method was applied satisfactorily to the determination of propranolol in a commercial formulation and no eventual interferent effects of the formulation excipients exist.

First of all, the samples were analyzed using the phosphorimetric method described above. The concentration obtained was 9.89 mg/tablet (recov-

Table 2
Analytical parameters of proposed method

Slope	0.0103
Standard deviation of slope	0.0059
Intercept	0.0021
Standard deviation of intercept	0.00001
Correlation coefficient	0.9993
Linear range (ng ml^{-1})	0–500
Sensitivity (ng ml^{-1})	6.7
Detection limit (ng ml^{-1})	14.4
Quantification limit (ng ml^{-1})	48.0
R.S.D. (%)	
100 ng ml^{-1}	4.31
200 ng ml^{-1}	2.10
300 ng ml^{-1}	1.36
400 ng ml^{-1}	1.10
500 ng ml^{-1}	0.96

ery percentage of 98.8%) and a RSD of 0.6%. Also, the method was validated with a standard addition method of calibration. To check the similarity of the slopes, a Student t-test is used [26] and it was confirmed that the slopes are essentially the same. In this case, the concentration obtained was 9.77 mg/tablet (recovery percentage of 97.7%).

No interferences were detected because the phosphorescence intensity and emission spectra were the same in solution with or without pharmaceutical preparation, and the standard calibration and standard addition calibration have the same slope.

4. Conclusions

In this work, it has been demonstrated that the heavy atom-induced room-temperature phosphorimetry methodology enhances the sensitivity and selectivity for the analysis of small amounts of chemicals in real samples. The proposed method can be recommended for the routine determination of propranolol in pharmaceutical preparations, as it is rapid and simple, and the results obtained showed good precision. This methodology could be extended to other drugs or chemicals with a naphthalene nucleus.

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