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Kinetic determination of propranolol in tablets by oxidation with ceric sulphate

SALAH M SULTAN,*† SAAD A ALTAMRAH,‡ ABDULLAH M AZIZ ALRAHMAN,‡ IBRAHIM Z ALZAMIL‡ and MOHAMMED O KARRAR‡

† *Chemistry Department, King Fahd University, KFUPM Box 2026, Dhahran 31261, Saudi Arabia*
‡ *Department of Chemistry, College of Science, King Saud University, Riyadh 11451, P O Box 2455, Saudi Arabia*

Abstract A simple and accurate kinetic method for the determination of propranolol has been developed Cerium(IV) sulphate (0 5 M) is used to oxidize propranolol in 2 M sulphuric acid at room temperature to the ketone form that absorbs light at a λ_{max} of 525 nm The fixed-concentration method is used by recording the exact time, t(s), taken for the reaction to reach a fixed absorbance of 0 100 The unknown concentration, c(M), of propranolol is calculated from the equation

$$1/t = 0\ 0\ 000217 + 0\ 03\ c$$

The method has been applied to the determination of propranolol in proprietary tablets and the results were compared with those obtained by the B P and other standard methods

Keywords *Kinetics, fixed-absorbance method, propranolol determination*

Introduction

Propranolol hydrochloride, 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride, is commonly used as a β-adrenergic blocking agent that inhibits the effect of catecholamines released in the heart It is prescribed for its antihypertensive, antianxiety, anticonvulsant, antianginal and antiarrhythmic effects [1–3], it has also been proposed for use in disfunctional labour and migraine [4, 5] Various methods for the determination of propranolol have been described, including fluorimetry [6, 7], spectrophotometry [8, 9] and commonly chromatography [10–18] The B P [19] monograph described a method for the determination of propranolol in non-aqueous media, the drug was dissolved in methanol in a standard flask and the resulting solution was determined spectrophotometrically at 290 nm Recently, Sultan [1] determined propranolol kinetically by the fixed-time method by oxidation with potassium dichromate in 5 M sulphuric acid and heating the reactants at 90°C for 20 min, the absorbance (A) of the resulting product of chromium(III) was measured at 590 nm The propranolol concentration (c) was calculated from the equation

$$A = 0\ 000857 + 0\ 000564\ c$$

*To whom correspondence should be addressed

In the present paper, propranolol is determined by the fixed-concentration method, the drug is reacted with cerium(IV) in 2 M sulphuric acid at room temperature When the fixed preselected absorbance at 525 nm of the oxidized form of propranolol is attained, the time is recorded and the unknown concentration of propranolol is calculated from the corresponding equation of the calibration graph

Experimental

Reagents and samples

Chemicals of analytical or pharmaceutical grade were employed throughout, together with high purity water

Cerium(IV) solution A stock solution of 0 01 M $Ce(SO_4)_2$ was prepared in 0 5 M sulphuric acid

Sulphuric acid A stock solution (10 M) was prepared in the usual way

Propranolol standard solution (1 mg ml^{-1}) This was prepared by dissolving 500 mg of propranolol hydrochloride (kindly supplied by ICI, batch ref No 8297/85 and 99 8%, m/m purity) in about 200 ml of warm water, the solution was stirred for 5 min, cooled to room temperature and diluted to volume in a 500-ml standard flask

Propranolol tablets, (1 mg ml^{-1}) Ten tablets were weighed accurately and crushed into fine powder A quantity of this powder, equivalent to 500 mg of propranolol, was weighed accurately and dissolved in about 50 ml of hot chloroform, the solution was stirred for 5 min, filtered through a Whatman No 41 filter-paper and evaporated to dryness The residue was dissolved in about 200 ml of hot distilled water for 5 min, cooled and made up to volume with water in a 500-ml standard flask

Apparatus

A Beckman Model 35 spectrophotometer connected to a Beckman Model 24–25 ACC recorder was used for all spectrophotometric measurements Matched sets of cells (w 210/UV 10 00 mm) were used

Results and Discussion

Optimization and kinetics

The oxidation of propranolol with cerium(IV) was explored thus confirming information on its reaction mechanism and extending knowledge on its chemical behaviour, this was done with the aim of finding an alternative and simple method for its determination by kinetic methods of analysis under the true conditions of the reaction Cerium(IV) was found to react slowly with propranolol producing a brown-red colour that absorbs at a λ_{max} of 525 nm, the formation of which is the basis of this method, the coloured product is believed to be the oxidized form of propranolol, produced when oxidized anodically [20] The rate of formation of this product is followed spectrophotometrically and found to be dependent upon acidity, temperature and concentrations of reactants

The rate of the reaction was found to increase as sulphuric acid concentration was

increased The rate of reaction was moderate at 1 5–2 5 M sulphuric acid, i e it was too fast to record measurements above this range and too slow to follow below this range Thus 2 M sulphuric acid was found to be acceptable

Similarly, a rise in temperature accelerated the reaction but the solution became turbid and a fine precipitate settled as the temperature was increased To avoid this complication, the reaction was conducted at 25°C, at which temperature the reaction rate was measurable

Obviously, a higher concentration of cerium(IV) than that of propranolol is mandatory so that the rate of its change could be constant when compared with that of the latter It was found that 0 001 M of cerium(IV) is the limiting concentration above which the absorbance of the cerium(IV) overlaps that of the product

The influence of change of propranolol concentration on the reaction rate is illustrated in Fig 1 which clearly indicates that the rate increases significantly as the propranolol concentration increases Therefore, the concentration range of propranolol determination is limited by the suitable preselected fixed absorbance that intersects and falls within the measuring rates In the present experiments propranolol can be determined in the range 70–200 μg ml^{-1}

It is concluded that the optimum conditions for the determination of propranolol in the range 70–200 μg ml^{-1} are 2 M sulphuric acid, 0 001 M cerium(IV) sulphate, and room temperature (25°C)

Under such conditions the concentration of propranolol is at least 1/10 of those of cerium(IV) and that of sulphuric acid, hence the reaction would follow pseudo-zero-order kinetics with respect to both cerium(IV) and sulphuric acid The rate in this case would be directly proportional to propranolol concentration and would follow a pseudo-first-order rate equation

$$\text{Rate} = \frac{\Delta A}{\Delta t} = k'[\text{propranolol}]^n, \qquad (1)$$

where k' is the pseudo-first-order rate constant and n is the reaction order with respect to propranolol

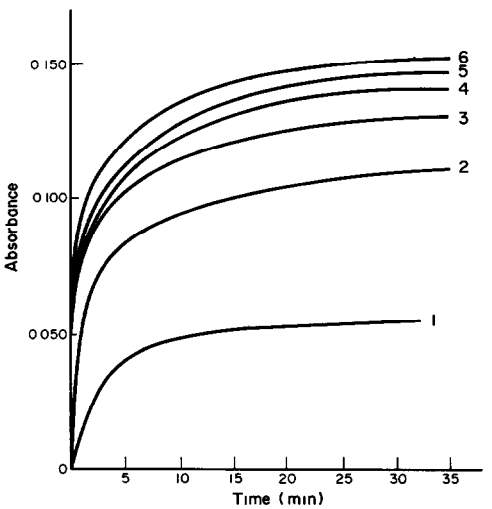

Figure 1
The effect of propranolol concentration on the reaction rate Graphs 1–6 represent propranolol concentrations of 80, 100, 120, 140, 160 and 180 μg ml^{-1}, respectively

From Fig 1 it is clear that the reaction takes place in two steps the first step is very fast and the second one is slow and rate determining From the rates of the second step and by regression of a plot of $\log_{10}$ of absorbance versus time (s), a straight line is obtained with a correlation coefficient (r) = 0 99 and slope (k') = s^{-1} indicating that the kinetics of the reaction, with respect to propranolol (n), are first order The constancy of the values of k' for different propranolol concentrations is given in Table 1 thus confirming a first-order reaction

Proposed mechanism

Previous investigations [1, 20] showed that the *N*-alkylethanolamine group is the common active site of the propranolol molecule From the results for the reaction of propranolol with cerium in excess, the observation of two steps in the reaction could be explained by the occurrence of two consecutive steps in the oxidation of the hydroxyl function In the first step, a radical is formed by releasing one hydrogen atom in a reversible fast reaction In the second step, a ketone is formed and hydrogen is released, this represents the slow rate-determining step The phenomenon that the reaction rate is accelerated by an increase in sulphuric acid concentration and retarded by a decrease in sulphuric acid concentration, could be explained by the release of the free protons in both steps of the reaction to form the ketone The following scheme represents the proposed mechanism and is in full agreement with results of previous studies [1, 20]

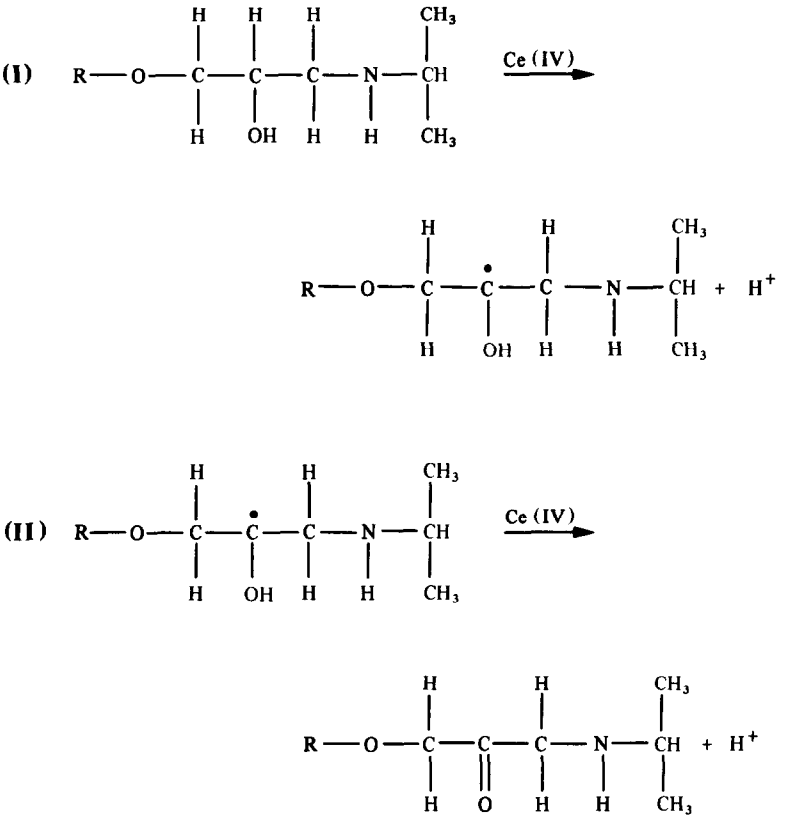

Table 1
Values of the reaction rate constant (k') for the reaction at various concentrations of propranolol and at constant concentrations of 2 M sulphuric acid and 0 001 M cerium(IV) sulphate at 25°C

Propranolol ($\mu g\ ml^{-1}$)	k' (s^{-1})
70	$4\ 19 \times 10^{-5}$
80	$4\ 37 \times 10^{-5}$
100	$4\ 41 \times 10^{-5}$
120	$4\ 21 \times 10^{-5}$
140	$4\ 33 \times 10^{-5}$
150	$4\ 46 \times 10^{-5}$
170	$4\ 51 \times 10^{-5}$
180	$4\ 39 \times 10^{-5}$
200	$4\ 29 \times 10^{-5}$

where R is the residue of the propranolol molecule and represents two conjugate benzene rings

Appraisal of the kinetic method

Rates were measured by recording absorbance–time graphs (Fig 1) for the reaction at constant concentrations of 2 M sulphuric acid and 0 001 M cerium(IV) sulphate at 25°C but with different concentrations of propranolol These graphs were treated by the fixed-concentration method in which a value of absorbance is preselected and time is measured The fixed absorbance is preselected so that it intersects graphs of the widest range of concentration possible At a fixed absorbance, equation (1) could be rearranged as follows

$$1/t = k'[\text{propranolol}] \tag{2}$$

In this method, an absorbance of 0 100 was found to be suitable in that it covers a wide range of 70–200 $\mu g\ ml^{-1}$ of propranolol Therefore the reciprocal of time t (s) versus propranolol concentration (M) (Table 2) was plotted by a computer and the following equation of the calibration graph was obtained

$$1/t = 0\ 000217 + 0\ 03c,\ r = 0\ 995, \tag{3}$$

Table 2
Values of reciprocal of time (s^{-1}) calculated at a fixed absorbance of 0 100 for different concentrations of propranolol at constant concentrations of 2 M sulphuric acid and 0 001 M cerium(IV) sulphate at 25°C

$1/t(s^{-1})$	Propranolol (M)
75	$1\ 33 \times 10^{-2}$
120	$8\ 33 \times 10^{-3}$
180	$5\ 56 \times 10^{-3}$
240	$4\ 17 \times 10^{-3}$
900	$1\ 11 \times 10^{-3}$

Table 3
Results of analysis of proprietary tablets of propranolol by the fixed-concentration method compared statistically with those obtained by the B P method

Proprietary name	Supplier	Nominal weight (mg propranolol/tablet)	% Recovery ± SD* Present method	% Recovery ± SD* B P method	Calculated value of t†
Inderal	ICI, England	10	100 1 ± 0 8	99 8 ± 0 4	0 84
		40	99 9 ± 0 7	99 8 ± 0 3	0 32
		80	99 8 ± 0 6	99 9 ± 0 4	0 37
		160	99 8 ± 0 9	100 1 ± 0 6	0 75
Inderal	Ayrest, Canada	80	99 8 ± 0 6	99 9 ± 0 7	0 37
Propranolol	Charnwood, USA	10	99 9 ± 0 8	100 1 ± 0 4	0 56
		40	99 5 ± 0 7	99 4 ± 0 5	0 32
		80	99 9 ± 0 7	100 1 ± 0 4	0 64
Indecardine	Arab Pharm Man Co , Jordan	10	99 72 ± 0 61	99 31 ± 0 54	1 50
		40	99 4 ± 0 7	99 5 ± 0 6	0 32

*Standard deviation (SD) for five determinations based on label claim
†Theoretical value at 95% confidence level = 2 78

where c is the initial concentration of propranolol (M) The initial rate, the rate constant and the fixed-time methods [21, 22] were applied, but were not fruitful

Applications and comparison with other methods

The method was applied to the determination of propranolol in proprietary tablets by using equation (3) The same batches of tablets, listed in Table 3, were analysed by the B P method [19] and the results obtained by both methods were statistically compared by calculating the Student t-test values From the results, it is clear that the t-test values do not exceed the theoretical value of 2 78 for the 95% confidence level indicating no significant difference between the two methods Excipients in the dosage forms tested, did not cause any interference In addition the presence of chloride (in the drug) did not interfere This was checked by analysing a chloride-free drug sample prepared by converting propranolol hydrochloride into the sulphate using a column charged with Amberlite IRA 400 (Cl) anion-exchange resin and washed first with 0 04 M sodium sulphate (analytical grade) and finally with water

The new method is more specific than the B P method [19] and other UV spectrophotometric methods [6–9] in which the reaction takes place in non-aqueous media The proposed method is rapid and simple and allowed the determination of more proprietary tablets than did the fixed-time method which requires heating the reactants at 90°C for 20 min In addition, the method does not need tedious extraction procedures as those used in the chromatographic methods [10–18]

Recommended procedure

To an appropriate amount of propranolol in a 50-ml standard flask add 5 ml of cerium(IV) stock solution and 7 5 ml of the stock solution of sulphuric acid then make up to volume with water Start a stopwatch and shake the flask gently Transfer some of the reaction solution into the photocell and follow the absorbance at 525 nm against the reagent blank treated similarly Record precisely the time when the absorbance exactly reaches 0 100 Finally, calculate the unknown concentration of propranolol by substituting into the following equation

$$1/t = 0\ 000217 + 0\ 03c,$$

where t = time (s) and c = concentration of propranolol (M)

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