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Cerimetric Determination of Propranolol in Bulk Drug Form and in Tablets

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Two simple, accurate and precise methods are described for the determination of propranolol hydrochloride with cerium(IV) sulphate. The titrimetric method is based on the oxidation of the drug by a known excess amount of cerium(IV) sulphate and back titration of the unconsumed oxidant with ammonium ferrous sulphate. In the spectrophotometric method, the unreacted cerium(IV) sulphate is treated with iron(II) sulphate, and the iron(III) sulphate produced is complexed with thiocyanate and measured at 480 nm, thereby permitting the determination of the amount of unreacted cerium(IV) sulphate. In both procedures, the amount of the reacted oxidant corresponds to the drug content. Different variables affecting the reaction between propranolol and cerium(IV) sulphate were studied and optimised. In titrimetry, the reaction stoichiometry which formed the basis for calculations was established. At 480 nm, Beer's law is obeyed for 0-5 μg mL^{-1} of propranolol hydrochloride. The molar absorptivity and Sandell sensitivity of the procedure were calculated in addition to limits of detection and quantification. Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures. The procedures described were successfully applied to the determination of propranolol hydrochloride in bulk drug form and in tablets.

Key Words: Propranolol, titrimetry, spectrophotometry, cerium(IV) sulphate, iron(III), thiocyanate.

Introduction

Propranolol hydrochloride[1] PPH, (t)-1-Isopropyl amino-3-(1-naphthyloxy propan-2-ol) hydrochloride, whose structure is given in Figure 1, is a beta adrenergic blocker. It is used as an antihypertensive, antianginal and antiarrhythmic agent. Various methods suggested for its determination include high-performance liquid chromatography (HPLC)[2−4], reversed phase HPLC[5], liquid chromatography[6], thin layer chromatography[7], UV spectrophotometry[8−10], visible spectrophotometry[11−18], fluorimetry[19], phosphorimetry[20] and voltammetry[21]. Chromatographic and luminescence techniques involve an expensive experimental set up and are not always easily available. Spectrophotometric methods based on a charge-transfer complexation reaction[11]

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use organic solvents as the reaction medium. Methods using nitration[12], nitrosation[13], redox[14,15] and redox-complexation reactions[16] require heating of the reaction mixture for 20-30 min and employ very high sulphuric acid concentrations[13]. The chief limitation of the method using the colour reaction with N-bromosuccinimide and celestine blue[17] is that the latter is never available in a pure state and the results are not reliable, since that method is based on the measurement of absorbance of celestine blue. The indirect spectrophotometric method[18] also uses N-bromosuccinimide and the coloured species measured is less stable. Furthermore, the working conditions are highly critical.

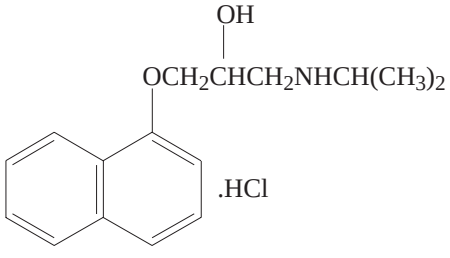

Figure 1. Structure of PPH.

Only three titrimetric procedures, visual[22], a-c oscillopolarographic[23] and conductometric[24] employing N-bromosuccinimide, sodium tetraphenyl borate and ammonium reineckate, respectively, as reagents are reported for the assay of propranolol. The present investigation was undertaken with the aim of developing new, simple, rapid and accurate methods, free from many of the drawbacks usually encountered in other methods, for the analysis of propranolol hydrochloride in bulk drug form and in various formulations. The methods are based on the oxidation of the drug by a known excess amount of cerium(IV) sulphate in acid medium, and the determination of the unreacted oxidant by back titration with ammonium ferrous sulphate or by spectrophotometry after treatment with iron(II) sulphate and complexing the iron(III) sulphate produced with thiocyanate.

Experimental

Apparatus

A Systronics model 106 digital spectrophotometer with matched glass cells was used for the absorbance measurements.

Reagents and materials

All chemicals used were of analytical reagent grade. Distilled water was used throughout the investigation.

A standard cerium(IV) sulphate (0.05 M) was prepared in 1 M suphuric acid and standardised with ammonium ferrous sulphate[25]. Lower concentration solutions were obtained by appropriate dilution. Sulphuric acid (10 M) was prepared by adding 140 mL of concentrated acid to 110 mL of water with cooling. Ferroin indicator was prepared by dissolving 1.485 g of 1,10-phenanthroline in 100 mL of 0.025 M ferrous sulphate. A 1 M ammonium thiocyanate solution was prepared by dissolving 7 g of the reagent in water and diluting to 100 mL with water. A 0.02 M ammonium ferrous sulphate solution was prepared by dissolving 15.696 g of the reagent in 5 mL of 1 M sulphuric acid and diluting to 2 L in water. A 1 mg mL^{-1} PPH solution was prepared in water.

Analytical Procedures

Titrimetry

A 10 mL aliquot of the drug solution containing 1-7 mg of PPH was transferred into a titration flask, and made acidic by adding 2.0 mL of 10 M sulphuric acid. Then, 10 mL of 0.02 M cerium(IV) sulphate was added by means of a pipette and the contents were mixed well. The flask was kept aside for 10 min with occasional shaking, and two drops of ferroin indicator were added and the contents were titrated with 0.02 M ammonium ferrous sulphate until the appearance of red. A blank was run in the same way with 10 mL of water. The amount of PPH was found from the volume of cerium(IV) sulphate solution reacting with the drug.

Spectrophotometry

In each of a series of 10 mL standard flasks were placed 0.0-2.5 mL of 20 μg mL^{-1} PPH followed by the addition of 1 mL of 5 M hydrochloric acid and 1 mL of 250 μg mL^{-1} cerium(IV) sulphate, and the overall volume was adjusted to 5 mL by adding a requisite volume of water. The flasks were let stand for 15 min with occasional shaking. Subsequently, 1 mL of 400 μg mL^{-1} ammonium ferrous sulphate was added to each flask and the contents were mixed well. After 1 min, 3 mL of 1 M ammonium thiocyanate were added and the volume was made up to the mark, and the absorbance was recorded at 480 nm against a water blank. The concentration of the drug in an unknown solution was read from the calibration graph or computed from the regression equation.

Procedure for tablets

Twenty tablets were weighed and ground into a fine powder. A portion of the powder equivalent to 100 mg of PPH was accurately weighed into a 100 mL calibrated flask, 60 mL of water was added and the contents were shaken thoroughly for about 20 min to extract the drug. The contents were diluted to the mark, mixed well and filtered using a quantitative filter paper to remove insoluble residue. A suitable aliquot of filtrate was used for titrimetric analysis. The filtrate containing 1000 μg mL^{-1} of PPH was diluted stepwise to obtain 20 μg mL^{-1}, and an appropriate aliquot was subjected to analysis by spectrophotometry using the procedure described above.

Results and Discussion

Both methods are based on the oxidation of PPH with a known excess of cerium(IV) sulphate and the determination of the unreacted oxidant by titrimetry or spectrophotometry.

Titrimetry

A study of the optimum conditions was carried out and the stoichiometry of the reaction of PPH with cerium(IV) sulphate was ascertained. The conditions optimised were the choice of medium (for the quantitative reaction), the time required for the reaction to be completed and the amount of reagent. Under optimum conditions, each mole of PPH was found to react with 5 moles of cerium(IV) sulphate. A 2 mL solution of 10 M sulphuric acid in a total volume of 22 mL was found suitable for the quantitative oxidation

of the drug in 10 min at room temperature (30 ± 2 °C). For the range (1-7 mg) of PPH studied, 10 mL of 0.02 M cerium(IV) sulphate was found adequate for the quantitative reaction. The reaction was found to be slow at lower acid concentrations. When the contact time exceeded 10 min, reaction stoichiometry was found to be slightly altered.

Spectrophotometry

The proposed spectrophotometric method is based on the oxidation of PPH by a known excess of cerium(IV) sulphate in hydrochloric acid medium, treating the unreacted oxidant with iron(II) sulphate and determining the iron(III) sulphate formed by complexing with thiocyanate, and measuring the absorbance of the complex at 480 nm. PPH, when added in increasing amounts, consumes cerium(IV) sulphate for its oxidation. Consequently, there is a concomitant fall in cerium(IV) sulphate concentration. When unreacted cerium(IV) sulphate is reduced by a fixed amount of iron(II) sulphate, there will be a concomitant decrease in iron(III) sulphate concentration formed. This is observed as a proportional decrease in the absorbance of iron(III) sulphate-thiocyanate complex on increasing the concentration of PPH (Figure 2). The absorbance is found to decrease linearly with increasing concentrations of PPH and this forms the basis for the determination of drug. The reaction scheme is presented in Figure 3.

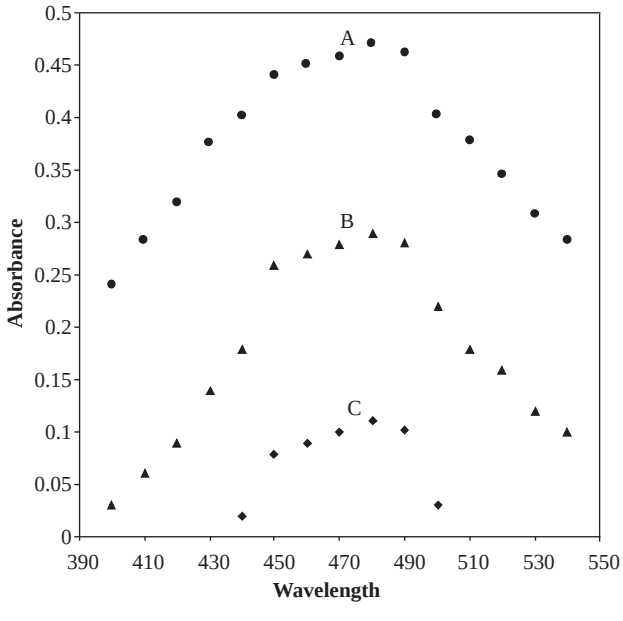

Figure 2. Absorption Spectra of: A. Blank containing 250 μg Ce(IV) sulphate in 10 ml B. and C.Reaction mixture of 250 μg Ce(IV) sulphate after treatment with 20 μg and 40 μg of PPH, respectively, in 10 ml.

Two blanks were prepared for this study. The reagent blank containing optimum concentrations of all the reagents except PPH gave maximum absorbance (Figure 2). The other blank was prepared in the absence of cerium(IV) sulphate and PPH to determine the contribution of other reagents to the absorbance of the system. Since the absorbance of the second blank was negligible, the absorbance of the developed colour was measured against water. Neither the oxidation product of PPH nor the cerium(III) produced in the reaction interfered in the absorbance measurement at 480 nm.

$$\text{Propranolol} + \text{Ce(IV)} \xrightarrow{H^+} \text{Oxidation product} + \text{Unreacted Ce(IV)} + \text{Ce(III)}$$

$$\text{Unreacted Ce(IV)} + \text{Fe(II)} \xrightarrow{H^+} \text{Ce(III)} + \text{Fe(III)}$$

$$\text{Fe(III)} + \text{SCN}^- \longrightarrow \underset{\text{red}}{\text{Fe(SCN)}^{2+}}$$

Figure 3. Reaction scheme showing formation of measured colour.

Optimisation of reaction conditions

The conditions for the determination of iron(III) sulphate with thiocyanate are well established[26]. Hence, the various parameters involved in the oxidation of the drug by cerium(IV) sulphate and subsequent reduction of unreacted oxidant by iron(II) sulphate were optimised. Although, nitric or hydrochloric acid medium could be used for the complexation of iron(III) sulphate with thiocyanate, hydrochloric acid was selected because nitric acid, an oxidising agent itself, is likely to interfere with the oxidation of PPH by cerium(IV) sulphate. Sulphuric acid medium although convenient for the oxidation of PPH by cerium(IV) sulphate was not preferred since it reduces the colour intensity of iron(III) sulphate-thiocyanate complex[26]. A 1 mL volume of 5 M hydrochloric acid was found adequate for the oxidation of PPH by cerium(IV) sulphate, as well as for the subsequent steps of reduction of cerium(IV) sulphate by iron(II) sulphate and complex formation of iron(III) sulphate produced with thiocyanate.

Because of non-linearity at higher concentrations[26], 6 μg mL^{-1} of iron(III) was taken as the upper limit that could be determined by the thiocyanate method. Stoichiometrically, 223.0 μg of cerium(IV) sulphate would be required to produce 60 μg of iron(III) from 518.2 μg of ammonium ferrous sulphate. However, slightly large amounts, 250 μg of cerium(IV) sulphate and 400 μg of ammonium ferrous sulphate, were employed to ensure a quantitative reaction. Though a fixed amount of ammonium ferrous sulphate is not really required, large amounts are undesirable since iron(II) sulphate tends to undergo aerial oxidation producing deviant results. Hence, a fixed amount of ammonium ferrous sulphate (400 μg), enough to reduce the total cerium(IV) sulphate (250 μg) used, was employed in the investigation.

The oxidation of PPH by cerium(IV) sulphate was complete in 15 min but the subsequent oxidation of iron(II) sulphate to iron(III) sulphate by unreacted cerium(IV) sulphate and the complexation of the resulting iron(III) sulphate with thiocyante were instantaneous under the optimum conditions described. The developed colour was stable for more than 30 min.

Analytical data

Titrimetry was found to be applicable in the range 1-7 mg. Outside these limits deviant results were obtained, besides taking more time for quantitative reaction if the upper limit exceeded 7 mg. The relationship between the titration end-point and the drug amount was evaluated by calculating the correlation coefficient value, r, via linear least squares treatment and was found to be -0.9864 indicating that the reaction between PPH and cerium(IV) sulphate proceeds stoichiometrically in the ratio of 1:5.

Beer's law is obeyed in the range 0-5 μg mL^{-1}. The apparent molar absorptivity and Sandell sensitivity values are 3.6×10^4 L mol^{-1} cm^{-1} and 8.06 ng cm^{-2}, respectively. The linear plot gave the regression

equation:

$$A = 0.4657 - 0.0883C$$

where A is the absorbance and C concentration in μg mL^{-1}, and with a correlation coefficient of -0.9994 (n = 6). The limits of detection and of quantification were 0.0303 μg mL^{-1} and 0.1021 μg mL^{-1} respectively.

Accuracy, precision and ruggedness

To ascertain the accuracy and precision of the methods, seven replicate determinations on the same solution containing four different levels of PPH were performed. The percent error, RSD and range of error at 95% confidence level which are presented in Table 1, indicate the high accuracy and precision of the methods.

Table 1. Evaluation of accuracy and precision of the methods.

Titrimetry					Spectrophotometry				
PPH taken, mg	PPH found*, mg	Error, %	RSD, %	Range of error, %	PPH taken, μg	PPH found*, μg	Error, %	RSD, %	Range of error, %
1.00	0.99	1.01	2.50	2.50	20.00	19.54	2.30	2.67	2.67
3.00	2.99	0.33	1.00	1.00	30.00	30.04	0.13	0.44	0.44
5.00	5.00	0.00	0.60	0.60	40.00	39.96	0.10	0.15	0.15
7.00	7.01	0.14	0.43	0.43	50.00	50.49	0.98	0.20	0.20

*Mean value of seven determinations.

To determine the ruggedness of the methods, four replicate determinations at four different levels of the drug were carried out. The within-day RSD values were less than 2.5%. The values of between-day RSD for four different levels of the drug, obtained from determinations carried out over a period of 4 days, are given in Table 2 and are indicative of the reasonable reproducibility of the methods.

Table 2. Between-day precision of the determination of PPH by the proposed methods.

Titrimetry			Spectrophotometry		
Amount taken, mg	Amount found, mg	RSD*, %	Amount taken, μg	Amount found, μg	RSD*, %
1.00	0.99	2.50	20.00	19.74	1.89
3.00	2.92	1.02	30.00	30.15	2.91
5.00	4.95	0.98	40.00	40.15	2.58
7.00	6.98	1.50	50.00	50.38	2.45

*Values obtained for four determinations over a period of 4 days.

Interferences

In pharmaceutical analysis, it is necessary to test the selectivity towards excipients and fillers added to pharmaceutical preparations. Commonly encountered excipients such as starch, talc, glucose, alginate and stearate did not interfere in the proposed methods. This is clear from the results obtained for pharmaceutical formulations (Table 3).

Table 3. Results of analysis of PPH in tablets by the proposed methods.

Tablet brand name*	Label claim, mg per tablet	Found$^{\psi}$, % recovery ± SD			Student's t- test^{x}		F-test^{y}	
		Titrimetry (T)	Spectrophotometry (S)	Reported method[9]	T	S	T	S
B.P. Norm[a]	40.00	98.55 ± 0.85	100.15 ± 0.74	99.18 ± 0.42	0.67	0.60	4.09	3.10
Betablock[b]	10.00	101.60 ± 1.26	100.12 ± 0.86	100.56 ± 1.04	1.09	0.95	1.46	1.46
Betacap[c]	80.00	97.65 ± 2.64	98.16 ± 1.34	98.74 ± 0.85	1.96	1.12	9.64	2.48
Ciplar[d]	10.00 40.00	98.90 ± 1.35 101.65 ± 1.62	100.34 ± 0.95 103.12 ± 1.26	99.35 ± 1.26 102.26 ± 0.94	1.30 1.32	1.11 1.11	1.15 2.97	1.76 1.80
Corbeta[e]	40.00	103.24 ± 0.74	102.36 ± 1.55	101.94 ± 0.62	0.68	1.18	1.42	6.25
Inderal[f]	10.00 40.00 80.00	98.64 ± 1.26 97.58 ± 1.07 98.74 ± 0.88	100.80 ± 1.74 98.62 ± 0.63 100.03 ± 1.34	99.78 ± 0.84 99.03 ± 0.46 99.14 ± 0.63	1.07 0.82 0.76	1.37 0.55 1.05	2.25 5.41 1.95	4.29 1.87 4.52
Propal[g]	10.00 40.00	100.50 ± 1.75 101.46 ± 0.38	103.10 ± 0.96 102.34 ± 0.87	101.06 ± 0.78 100.38 ± 0.43	1.35 0.41	0.87 0.69	5.03 1.28	1.51 4.09

$^{\psi}$Mean value of five determinations

*Marketed by: a. Medley; b. USV; c. Nated; d. Cipla; e. Sarabhai; f. ICL; g. Sigma

^{x}Tabulated value at 95% confidence level is 2.78

^{y}Tabulated value at 95% confidence level is 6.39

Application to tablets

The proposed methods were applied to the analysis of PPH in tablets and the results were statistically compared with those obtained by a reported method[9]. When t- and F- tests at the 95% confidence level were applied, the calculated values of t and F did not exceed the theoretical values (Table 3). Therefore, there is no significant difference in the mean recoveries and precision between the proposed and reported methods.

Conclusions

The described methods allow the determination of propranolol in pure form and in formulated products. The experimental data are considered to indicate statisfactory specificity, linearity, accuracy, repeatability and sensitivity. The proposed titrimetric method has a couple of advantages over the direct titrimetric method proposed by Pathak et al.[22], who employed N-bromosuccinimide as the oxidimetric titrant. Cerium(IV) sulphate employed in the present method is stable for at least 6 months in 0.5 M sulphuric acid[27] whereas N-bromosuccinimide requires daily standardisation. Furthermore, although the method[22] is claimed to be

direct, it involves the iodometric back titration of any excess N-bromosuccinimide added beyond the methyl red end-point, thus making the procedure tedious and less reliable. The spectrophotometric method developed is the most sensitive of all the visible spectrophotometric methods[11−18] reported for PPH including the indirect methods based on iron(III)-thiocyanate[16] and N-bromosuccinimide-promethazine hydrochloride[18] reactions. The method of Zivanovic et al.[16] is far less sensitive with the linear range being 30-29,584 μg mL^{-1} (100 μM-0.1 M) and the method of Gowda et al.[18] employs an unstable oxidant solution, critical working conditions and less stable coloured species. In addition, the present spectrophotometric method, with the molar absorptivity and Sandell sensitivity values of 3.6×10^4 L mol^{-1} cm^{-1} and 8.06 ng cm^{-2}, respectively, is more sensitive than the recently reported method[18] ($\varepsilon = 1.36 \times 10^4$ L mol^{-1} cm^{-1} and Sandell sensitivity = 21.66 ng cm^{-2}). The described methods are rapid and reliable, and hence can be used for routine analysis.

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