ATOMIC ABSORPTION SPECTROMETRIC DETERMINATION OF PHENYLPROPANOLAMINE HCL IN PURE SOLUTION AND IN PHARMACEUTICAL PREPARATIONS BASED ON ION-PAIR FORMATION WITH SODIUM TETRAPHENYLBORON

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Abstract:

A new simple, rapid, accurate and precise method for the determination of phenylpropanolamine hydrochloride using atomic absorption spectrometry has been developed.

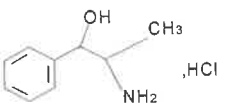
The method is based on precipitation of the ion-associate complex formed from the reaction of phenylpropanolamine hydrochloride drug with sodium tetraphenylboron reagent and the precipitate has been used for the quantitative analysis of the drug. The reacted boron in precipitate and the excess, unreacted, boron ions in the saturated solutions will be determined using direct and indirect atomic absorption spectrometry.

The precipitated ion associate was subjected to elemental analyses and metal content determination for elucidation of its structure. The effect of pH, ionic strength and temperature on precipitation was carefully studied and the solubility of the solid ion associate complex has been measured at optimum conditions and its solubility product was calculated. The present method has been successfully applied for the determination of the phenylpropanolamine hydrochloride drug in pure solution and in its pharmaceutical dosage forms.

From 2.82 to 56.31 mg per 25 ml solutions of this drug can be determined with recovery values of 95.74 - 99.04% and relative standard deviations (R.S.D.) 1.23-3.61% indicating a good precision and accuracy.

The results obtained were statistically compared to official method as revealed by F-and t-tests.

1. Introduction:



Phenylpropanolamine hydrochloride, $C_9H_{13}NO.HCl$ is largely an indirect-acting sympathomimetic. It is given by mouth for the symptomatic treatment of nasal congestion, so it is frequently used in mixed preparations for relief of cough and cold symptoms. Other uses of phenylpropanolamine hydrochloride include the control of urinary incontinence in some patients. It has also been used to suppress appetite in the management of obesity [1].

Several methods have been reported for the quantitative determination of phenylpropanolamine HCl. Among these are molecular spectrophotometries [2-7], Raman spectroscopy [8], NMR [9], potentiometry [10], conductimetry [11], GC-MS [12] and electrophoresis [13, 14].

Most of the analytical methods employed for determination of the studied drug are HPLC [15-22] which require complex and expensive equipment, provision for use and disposal of solvents.

Atomic absorption spectrometry occurs in the forefront of the most sensitive and widely used analytical techniques. In recent years, it has found wide applications for the determination of many important drugs [23-37].

Although atomic absorption spectrometry is a simple, rapid, sensitive, and reproducible method, it has not been reported yet in the literature to the determination of phenylpropanolamine hydrochloride drug.

The present study aims to develop atomic absorption spectrometric method for the determination of this drug. The method was performed by precipitating the cited drug with an excess of sodium tetraphenylboron as inorganic metal complex ion and determining the boron complex ions directly in the precipitate or indirectly in the filtrate using atomic absorption spectrometry.

2. Experimental:

2.1 Reagents and materials

All chemicals used were of analytical reagent or pharmacopeial grade. Double distilled water was used throughout for preparing all solutions. Authentic sample of phenylpropanolamine hydrochloride was provided by National Organization for Drug Control and Research, Giza, Egypt. Sodium tetraphenylboron and boric acid were Aldrich products. Sodium hydroxide and hydrochloric acid were used for adjusting the pH of the medium, while NaCl was used for adjusting the ionic strength. Pharmaceutical preparations assayed were purchased from local markets.

The following available commercial preparations were analyzed:

Conta-Flu tablets, (Egyptian International Pharmaceutical Industries Co., Cairo, Egypt) labeled to contain 24 mg phenylpropanolamine HCl per tablet.

Syphcornide, drops, (Syphco, Syrian Pharmaceutical Co., Damascus, Syria) labeled to contain 4 mg phenylpropanolamine HCl per ml.

Flurest, syrup, (Glaxo Wellcome Co., Cairo, Egypt) labeled to contain 2 mg phenylpropanolamine HCl per ml.

2.1.1. Preparation of the standard solutions:

A stock solution of phenylpropanolamine HCl, 0.1 M, was prepared by dissolving the accurately weighed amount of the drug in double distilled water and stored in dark bottle. More dilute solutions were prepared daily by appropriate dilution. Aqueous 0.3 M sodium tetraphenylboron solution was prepared by dissolving the accurately weighed amount in appropriate amount of double distilled water. Solutions of different pH values were prepared by using sodium hydroxide and hydrochloric acid solutions of concentration within the range 0.1-1.0 M and a 1.5 M of sodium chloride was used to prepare series solutions of different constant ionic strengths.

For AAS measurement, pure boric acid containing 3000 μg/ml was used to prepare a standard solution of boron in which appropriate volume of concentrated nitric acid was added. The solution, stored in a plastic bottle and it is stable for

approximately 6 months. Working standard solutions were prepared by suitable dilution of the stock solution.

2.1.2. Preparation of the ion-pair complex:

Phenylpropanolamine-tetraphenylboron ion-pair has been prepared by mixing solutions containing 10^{-2} M of sodium tetraphenylboron with the requisite amount of 10^{-2} M phenylpropanolamine HCl. The resulting precipitate was left in contact with its mother liquor over night to assure complete coagulation. The precipitated complex was filtered, washed with double distilled water till chloride free and dried at the room temperature. The composition of the ion-pair was found to be 1:1 as confirmed by elemental analysis and metal content data at the Microanalytical Center, Cairo University, Egypt.

2.2. Effect of pH, ionic strength and temperature:

To investigate the optimum conditions of precipitation, excess amounts of precipitate were added to three series of solutions having different values of pH, ionic strength and temperature.

In order to study the effect of pH on precipitation, ten 25 ml solutions covering the acid to alkaline range were prepared using 0.1 M HCl or NaOH to adjust different values of pH (1.0-10). To each solution, amount of precipitate was added. The mixtures were shaken, left to stand, filtered and the atomic absorbance was measured.

The same procedure was followed to study the effect of ionic strength, which 1.5 M of NaCl was used to prepare ten 25 ml solutions containing different concentrations (0.2-1.2 M) of NaCl.

The effect of the temperature was investigated by heating the mixtures in a water bath and the atomic absorbance was measured at different temperatures. The best values of pH, ionic strength and temperature were examined by measuring dissociated boron complex ion concentration. The optimum conditions are those in which the ion-pair exhibit the lowest solubility.

2.3. Determination of solubility of ion-pair complex:

The solid ion-pair was added in excess to a solution of the optimum pH and ionic strength. The solution was shaken for 5 – 6 hours and left to stand for a weak to attain equilibrium, then the saturated solution was filtered into a dry beaker (rejecting the first few ml of the filtrate) and six equal portions of this filtrate were taken. To three portions, a certain amount of boron standard solution was added and the atomic absorbance of the six samples was measured, which standard addition method was employed to evaluate the concentration of the boron complex ions and hence the solubility (S) and solubility product (Ksp)of the ion associate were calculated.

2.4. Sample preparation:

2.4.1. Authentic samples:

For analysis of pure solution, 30 ml of 0.1 M standard drug solution containing (563.10 mg) was pipetted into 100 ml calibrated flask and diluted to the mark with doubly distilled water. Aliquots of this solution containing (2.82-56.31 mg) of Phenylpropanolamine HCl were quantitatively transferred into 25 ml measuring flasks and then the general procedure was followed.

2.4.2 Pharmaceutical preparations:

For analysis of tablets, twenty tablets were weighed and powdered. An accurately weighed amount of the powder equivalent to fifteen tablets, approximately (360 mg of phenylpropanolamine HCl was dissolved, shaken, filtered to obtain clear solution, transferred into a 100 ml calibrated flask and diluted to the mark with redistilled water. Aliquots of this solution containing (3.60-36.00 mg) of phenylpropanolamine HCl were quantitatively transferred into 25 ml measuring flask and then the general procedure was followed.

For analysis of drops and syrup, certain volumes containing 4.0-20 or 4.0-40.0 mg of drops or syrup respectively, were pipetted into 25 ml volumetric flasks and the analysis was completed as in general procedure.

2.5. Apparatus:

Atomic absorption spectrometric measurements were carried out using a Smith-Itieftje 11, atomic absorption spectrometer. The fuel used was the acetylene and nitrous oxide. A boron hollow-cathode lamp was used under the following operation conditions: wavelength 249.7 nm, slit-width 0.7 nm, lamp current 10 mA. The pH values of solutions were measured using an Orion Research Model 601A digital pH-meter. All figures and calculations were carried out on computer using Microsoft excel 2003.

2.6. Calibration graphs of AAS:

A calibration graph was constructed using the standard boron solution previously prepared. Solutions having concentrations of (17.0-140 µg/ml) of boron were measured. Each measurement was performed at least four times to check the reproducibility. The obtained calibration graphs are straight lines passing approximately through the origin (Figure 1).

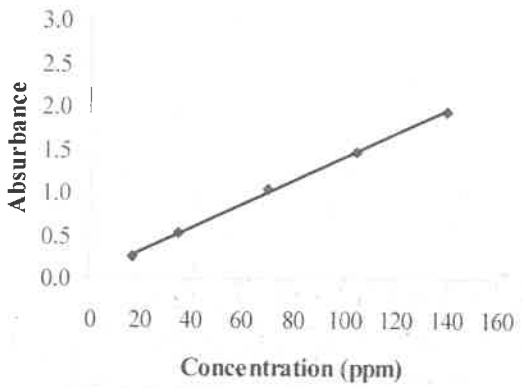


Figure 1. Atomic absorption calibration curve of B(III) ion concentrations.

2.7. General Procedure:

Aliquots (1.0–10.0 ml) of 3.0 x 10^{-2} M working standard solutions of phenylpropanolamine HCl were quantitatively transferred into 25 ml measuring flasks. To each flask 3.0 ml of 0.15 M standard solution of sodium tetraphenylboron was added and pH and ionic strength were adjusted to the desired values by using the required amount of 1.5 M NaCl, 0.1M HCl or NaOH, then made up to the mark with optimum pH and ionic strength solution The solutions are shaken well and left to stand for 30 min and then filtered through Whatman P/S filter paper (12.5 cm). The precipitate was washed thoroughly with redistilled water.

Direct Method: Accurately weighed amounts of the dried precipitate obtained above equivalent to (3.98-39.81 mg) of drug were dissolved in the least amount of ethanol and completed to 25 ml with redistilled water.

The absorbance of boron was measured at 249.7 nm against blank (omitting the addition of drug) and the boron concentrations were determined from the calibration curves. The reacted boron complex ion concentrations in the ion-pair, which equivalent to the drug concentrations, were calculated, and thus the concentration of phenylpropanolamine HCl was determined directly.

Indirect Method: The absorbance of the boron was measured using atomic absorption spectrometry (AAS) and the excess unreacted boron complex ion concentrations in the filtrates were determined. The consumed boron ion in complex ion-pair formation was calculated by subtraction. This value is equivalent to the phenylpropanolamine HCl concentration, and the drug concentration was thus calculated indirectly. A blank (omitting addition of drug) was prepared and the absorbance was measured at the same experimental conditions.

3. Result and Discution:

3.1 Ion-pair composition:

Phenylpropanolamine HCl gave coagulated precipitate with sodium tetraphenylboron. This precipitate forms the basis of the quantitative determinations of the phenylpropanolamine HCl drug. The equation for net reaction between phenylpropanolamine HCl and sodium tetraphenylboron is as follows:

$$C_9H_{13}NOHCl\ (aq) + C_{24}H_{20}BNa\ (aq) \longrightarrow C_9H_{13}NOH\text{-}C_{24}H_{20}B\ (s) + NaCl\ (aq)$$

Confirmation of the composition was performed using C, H, N and metal content elemental analysis. The values found are 83.86, 6.72, 2.94 and 2.27; while the calculated values are 84.00, 7.21, 2.97 and 2.29 for C, H, N and metal content respectively. The elemental analysis indicated that phenylpropanolamine HCl forms a 1:1 (drug: reagent) complex with sodium tetraphenylboron. The composition of this precipitate is in agreement with previous studies using potentiometric and conductometric methods [10, 11]

3.2. Optimization of ion-pair complex precipitation:

To select the optimum conditions, the effects of pH, ionic strength and temperature on the solubility of prepared ion associate complex were examined by measuring the atomic absorbance of boron complex ions and the solubility values were calculated using standard addition method of AAS. After comparing solubility of ion-pair at different values of pH, ionic strength and temperature, it was found that acid and alkali media have a solubilizing effect on the precipitate leading to

lower results for the direct technique and higher ones for the indirect technique. The optimum pH was found to be neutral media (pH = 7.0). Considering ionic strength effect on precipitation, 0.8 M of NaCl concentration was found to be the optimum value for the least solubility of the prepared ion-pair. Regarding the temperature effect on precipitation, the temperature range of about (20 - 60 °C) was found to be negligible effect. Higher temperature show relative solubilizing effect on the precipitate producing lower results for the direct technique and higher ones for the indirect technique.

Figure 2 shows optimum pH and ionic strength for the least solubility of the prepared ion associate complex. This mean that the formed complex is more stable and least soluble at pH = 7.0 and ionic strength = 0.8. There was no significant effect of temperature within the range of (20 - 60 °C).

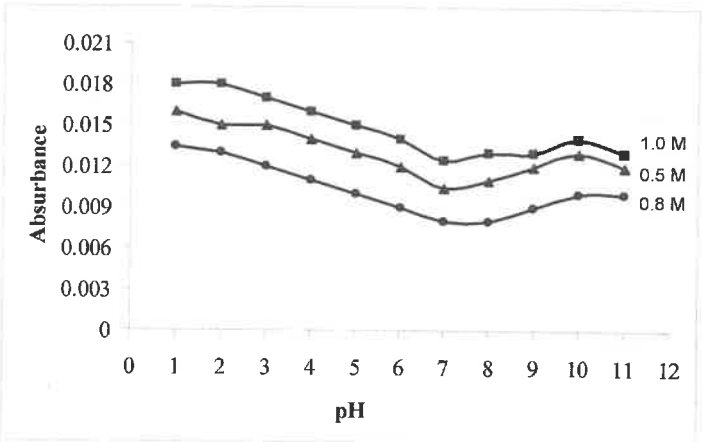


Figure 2. Effect of pH and ionic strength on solubility of phenylpropanolamine-tetraphenylboron ion-pair complex.

The solubility of the ion-pair was determined by putting a certain amount of the precipitate in the solution of required pH and ionic strength for several days. The amount of boron complex ion released was measured by standard addition method of AAS and then the solubility was calculated. A solubility value (S) of 1.21×10^{-3} M and a solubility product value (Ksp) of 1.47×10^{-6} were obtained, indicating a relatively good stability complex.

3.3. Atomic absorbance of boron:

Some previous reports found that, trace level of boron has low sensitivity and suitable matrix modifier was required to enhance the atomic absorbance of boron ions [38, 39]. However, in the present work, no modifier was needed to atomic absorbance measurements. The standard addition and calibration curve methods were successfully applied and the obtained values of absorbance signals were sufficient for the purposed determinations. The standard addition method was found to be more favorable at low concentration of boron.

3.4. Determination of phenylpropanolamine HCl in authentic samples and in pharmaceutical preparations:

As described in experimental section (2.1.), the boron contents can be determined either directly in the precipitate or indirectly in the filtrate by atomic absorption spectrometry, and thus, phenylpropanolamine HCl drug has been determined depending on the relation between its concentration and atomic absorption measurements obtained for the boron. The proposed method was applied under the optimum pH and ionic strength conditions to the determination of phenylpropanolamine HCl in pure solutions and in pharmaceutical preparations.

In pure solution phenylpropanolamine HCl was determined precisely and accurately over the concentration ranges 3.98 - 39.81 and 2.82 - 56.31 µg/ml for direct and indirect technique respectively, with recoveries in the range of 97.36 - 99.04 and relative standard deviation in the range of 1.23 - 2.15 (Table 1). The accuracy of the method was determined by investigating the recovery at ten concentration levels covering wide range of the authentic drug and three replicates of each concentration.

The concentration range of the proposed method indicates a relatively wide concentration range, the recoveries indicating good accuracy and the low values of relative standard deviation reflect the precision of the method.

Table 1. Determination of phenylpropanolamine hydrochloride in pure solutions and in pharmaceutical preparations by direct and indirect AAS.

	Direct			Indirect		
Samples	Taken (mg)	Recovery %	R.S.D. %	Taken (mg)	Recovery %	R.S.D. %
Pure solution	3.98-39.81	97.36-98.65	1.30-2.15	2.82-56.31	97.85-99.04	1.23-1.93
Conta-Flu (tablets)	7.80-36.00	96.13-98.24	2.07-2.81	3.60-36.00	96.30-98.51	2.01-2.74
Flurest (syrup)	8.00-20.00	96.15-98.40	2.54-3.11	4.00-20.00	96.03-98.66	2.16-3.47
Syphcomide (drops)	8.00-31.20	95.74-98.91	2.29-3.25	4.00-40.00	95.74-98.57	2.35-3.61

Pharmaceutical preparations including commercially available tablets, drops, and syrup containing 24 mg/tablet, 4 mg/ml and 2 mg/ml of phenylpropanolamine HCl respectively, were successfully analyzed. The concentration ranges, recoveries and relative standard deviations obtained for each pharmaceutical preparation are listed in Table 1. The accuracy was assessed by investigating the recovery of each of the pharmaceutical dosage form at seven concentration levels with three replicates of each concentration. The results attained by applying direct and indirect atomic absorption spectrometric method (Table 1) showed good recoveries and relative standard deviations which indicating good accuracy and precision.

The official method of phenylpropanolamine hydrochloride as reported In the British Pharmacopoeia is the titration method, which involves the titration of phenylpropanolamine HCl with 0.1 M NaOH with the endpoint determined potentiometrically [40].

The assay results obtained from the proposed method were statistically compared with those obtained from the official method using t- and F- tests.

As shown in Table 2, the calculated F-values at 95 % confidence level and t-values at 99.9 % confidence level are lower than the tabulated values (6.39 and 5.04) for F-

and t-test respectively. This means that the present method is of comparable precision to that of the official method and there is no significant difference between the mean values obtained by both methods.

3.5. Linearity of calibration graphs:

Under the experimental condition, AAS measurements for several series of standard solutions of boron ions were measured. Straight line calibration graphs between atomic absorbance and boron ion concentrations were obtained over a concentration range of 17-140 µg/ml (Figure 1).
The regression equation of the calibration curve was as follows:

$$A = 0.0137C + 0.0358,$$

Where A is the absorbance and C is the concentration in µg/ml. Calibration curve has correlation coefficient (R) higher than 0.999, indicating excellent linearity. Linearity was also checked by calculating the coefficients of determinations (R^2), the slopes (S) and the intercepts (I) of the calibration curves (Table 2).

Table 2. Linear regression of calibration curves and statistical treatment of results obtained for proposed and official methods.

Method	S	I	R	R^2	F-value	t-value
Direct	0.0137	0.0357	0.9996	0.9992	2.74	0.91
Indirect	0.0241	0.0326	0.9995	0.9990	3.50	2.18

S, I, R and R^2 are slope, intercept, correlation coefficient and determination coefficient respectively, for regression line of calibration curves.
F-test at 95% confidence limit, t-test at 99% confidence limit.

3.6. Selectivity

Since the formation of ion associate requires the existence of positively and negatively charged species, the presence of commonly encountered excipients added to the pharmaceutical preparations could be interfered with the desired drug.
In the present work, the ingredients and fillers do not impact used on this method. Thus, no extraction was needed to separate the desired compound from the drug matrix. The results were unaffected by the presence of excipients as shown by the good recoveries obtained when analyzing the studied drug in its dosage forms (Table 1). This indicates that the proposed method is selective enough for analysis of phenylpropanolamine HCl. in pharmaceutical dosage forms.

4. Conclusion

This paper reports a new example of ion associate complex application in drug analysis. The proposed direct and indirect atomic absorption spectrometric method is simple, rapid, selective and relatively sensitive compared to other analytical techniques. Therefore it is used successfully for determination of the phenylpropanolamine HCl drug either in its pure form or in its corresponding pharmaceutical preparations without interference from commonly used excipients
Student's t-test and F-test indicate the absence of systematic errors and no significant differences in precision between both proposed and official methods.

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