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Nonaqueous Titrimetric And Spectrophotometric Methods For The Assay Of Prochlorperazine In Pharmaceuticals

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ABSTRACT

Two simple, rapid and cost-effective methods based on titrimetry and spectrophotometry in non aqueous medium are described for the determination of prochlorperazine in pure form and in dosage forms. In titrimetry, the drug is dissolved in glacial acetic acid and titrated with acetous perchloric acid using, crystal violet being as indicator. Spectrophotometry involves adding different amounts of drug to a fixed amount of perchloric acid-crystal violet mixture and measuring the increase in absorbance at 570 nm. The titrimetric method is applicable over 4-20 mg range, and in spectrophotometry, Beer's law is obeyed over range 2.5-30 μg/ml. The apparent molar absorptivity is calculated to be 7.237 $\times 10^3$ l /mol /cm, with a Sandell sensitivity of 77.97 ng/cm^2. The limits of detection and quantification are calculated to be 2.30 and 0.76 μg ml^{-1}, respectively. Intra-day and inter-day precision and accuracy of the methods were evaluated as per ICH guidelines. The methods were successfully applied to the determination of PCPM in injection, the results were statistically compared with those of a reference method by applying Student's t-test and F-test. No interference was observed from common additives found in injection solution. The accuracy and reliability of the methods were further ascertained by parallel determination by a reference method and by recovery studies via standard-addition technique.

KEYWORDS

Prochlorperazine;
Determination;
Titrimetry;
Spectrophotometry;
Non-aqueous medium;
Dosage forms.

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INTRODUCTION

Prochlorperazine mesylate (PCPMs) (Figure 1) is an N-substituted phenothiazine derivative with a wide range of pharmacological actions. It is a potent neuroleptic and an anti-emetic. It is used in vertigo due to menire's syndrome, labyrinthitis and other causes, and for nausea and an anti-emetic. It is used in vertigo due to meniere's syndrome, labyrinthitis and other causes, and for nausea and vomiting from whatever causes. It may also be used for migraine, schizophrenia, and acute mania and as an adjunct to the short-term management of anxiety.

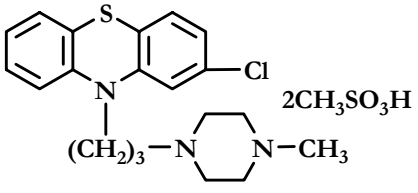

Figure 1: Structure of drug

A review of literature revealed that the determination of the drug in pharmaceuticals has been achieved by high-performance liquid chromatography[1-4], radioimmuno-assay[5], voltammetry[6], fluorimetry[7], titrimetry[8-11], uv-spectrophotometry[12] and visible spectrophotometry[13-24]. The reported titrimetric methods employed either highly acidic conditions or unstable titrant whereas spectrophotometric methods suffered from such limitations as extraction step and heating step in addition to lacking sufficient stability of the coloured species.

The paper describes the titrimetric and spectrophotometric determination of PCPM in bulk drug and in injection using non-aqueous medium. The methods, besides being sensitive, have been demonstrated to be both accurate and precise.

EXPERIMENTAL

Apparatus

A Systronics model 106 digital spectrophotometer with 1-cm matched quartz cells was used for absorbance measurements.

Reagents and Solutions

All chemicals used were of analytical reagent grade and all solutions were prepared in glacial acetic acid unless specified otherwise.

$HClO_4$- CV, indicator (1.5 mM $HClO_4$-0.25 mM crystal violet)

Prepared by mixing 15 ml 0.01 M perchloric acid and 10 ml of 1000 μg/ml crystal violet solutions and diluting to 100 ml with glacial acetic acid.

Standard drug solution

Pharmaceutical grade prochlorperazine mysealate was procured from Rhone-Poulene Ltd., India, as gift, and was used as received. A stock standard solution containing 2 mg/ml prochlorperazine mysealate was prepared by dissolving 500 mg of pure drug in glacial acetic acid and diluting to the mark in a 250 ml calibrated flask. This solution (2 mg/ml) was used for titrimetric work, and for spectrophotometric work, the same was diluted appropriately with glacial acetic acid to get 100 μg/ml working concentration.

Procedures

Visual titration (Method A)

A 10 ml aliquot of standard drug solution containing 4-20 mg of prochlorperazine mysealate was measured accurately and transferred into a clean and dry 100 ml titration flask, 2 drops of crystal violet indicator was added and titriated with standard 0.01 M perchloric acid to an emerald green end point. The amount of drug in the measured aliquot was calculated from

Amount (mg) = VMR

Where

V= volume of perchloric acid required, ml

M= relative molecular mass of drug,

R= molarity of perchloric acid.

Spectrophotometric assay (Method B)

Different aliquots (0.25-3.0 ml) of standard 100 μg/ml drug solution were accurately transferred into a series of 10 ml calibrated flasks. An exactly measured (2 ml) perchloric acid-crystal violet mixture was added to each flask and the volume was diluted to the mark with glacial acetic acid, mixed well and absorbance was measured at 570 nm against a re-

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agent blank. The increasing absorbance values at 570 nm were plotted against the concentration of drug to obtain the calibration graph. The concentration of the unknown was read from the calibration graph or calculated from the regression equation obtained from Beer's law data.

Procedure for dosage forms

The contents of twenty ampoules of stemetil injection were pooled in a clean and dry beaker, and an aliquot containing 200 mg of PCPMS was accurately measured and transferred into a 100 ml standard flask and diluted to the mark with glacial acetic acid and mixed well. An appropriate aliquot was then subjected to analysis by titrimetry. This solution equivalent to 2 mg/ml PCPMS was diluted appropriately to obtain 100 μg/ml drug solution and analysed by spectrophotometry as described under the general procedure.

RESULTS AND DISCUSSION

The present methods make use of the basic property of PCPMS and employ two techniques. The methods are based on the principle that substances, which are too weakly basic in aqueous medium, exhibit enhanced basicity in non-aqueous solvents thus allowing their easy determination. In the present titrimetric method, the weakly basic property of prochlorperazine was enhanced due to the non leveling effect of glacial acetic acid and titrated with perchloric acid with visual end point detection. Crystal violet gave highly satisfactory end point for the concentrations of analyte and titrant employed. The relationship between the drug amount and the titration end point was examined. The linearity between two parameters is apparent from the correlation coefficient of 0.9984 obtained by the method of least squares. From this, it is implied that the reaction between prochlorperazine and perchloric acid proceeds stiochiometrically in the ration 1:2 in the range studied, 4-20 mg.

Crystal violet is a dye exhibiting violet colour in the base form and emerald green in the acid form. The present spectrophotometrc method is based on the facts that the colour of the dye is dependent on the pH of the solution and that the colour change is not sudden but occurs continuously as the pH changes over a definite range. To a fixed amount of acid-dye mixture where the dye is in the acid form (emerald green), different amounts of PCPMS were added. This caused a progressive increase in pH of the solution because of neutralization of acid by the added drug (base), and as a result, the concentration of the acid form of the dye decreases. This is shown by the proportional increase in the absorbance of the solution at 570 nm which is corroborated by the correlation coefficient of 0.9998.

In a preliminary study, 20 μg/ml crystal violet in basic medium was found to exhibit a convenient absorbance at 570 nm. In the presence of 2 ml of 1.5 mM perchloric acid in a total volume of 10 ml, this absorbance decreased to a constant minimum. Hence, different amounts of drug were treated with a fixed amount of acid-dye mixture i.e., 2 ml of 1.5 mM $HClO_4$- 0.25 mM crystal violet (100 μg/ml) to determine the concentration range of the drug that could be determined by the method of absorbance transitions of the dye accompanying the pH changes. The dye colour was found to be stable for several hours, and the order of addition of reactants was not cririca l.

Analytical parameters of the spectrophotometric methods

A linear correlation was found between absorbance at λ_{max} and concentration of PCPM in the concentration ranges given in TABLE 1. The graphs showed negligible intercept as described by the regression equation,

$Y = a + bX$

(Where Y = absorbance of 1-cm layer of solution; a = intercept; b = slope and X = concentration in μg/ml). Regression analysis of the Beer's law data using the method of least squares was made to evaluate the slope(b), intercept(a) and correlation coefficient(r) for each system and the values are presented in TABLE 1. The optical characteristics such as Beer's law limits, molar absorptivity and Sandell sensitivity values of all the three methods are also given in TABLE 1. The limits of detection(LOD) and quantitation(LOQ) calculated according to ICH

TABLE 1: Analytical and regression parameters of spectrophotometric method

Parameter	Value
λ_{max}, nm	570
Beer's law limits, μg/ml	2.5 – 30
Molar absorptivity, l/mol/cm	7.24×10^3
Sandell sensitivity, μg/cm^2	0.0779
Limit of detection, μg/ml	0.76
Limit of quantification, μg/ml	2.30
Regression equation, Y*	
Intercept (a)	0.0003
Slope (b)	0.0150
Correlation coefficient, (r)	0.9998
S_a	0.0032
S_b	0.00012

***Y = a+bX, where Y is the absorbance and X concentration in μg/ml**
S_a. Standard deviation of intercept.
S_b. Standard deviation of slope.

guidelines[25] are also presented in TABLE 1 and reveal the high sensitivity of the spectrophotometric method.

Method validation

Accuracy and precision

To evaluate the accuracy and intra-day precision of the methods, pure drug solution at three different levels (concentrations) was analysed, each determination being repeated seven times. The relative error (%) and relative standard deviation(%) were less than 2.0 and indicate high accuracy and precision of the methods (TABLE 2). For a better picture of reproducibility on a day-to-day basis, a series of experiments was performed in which standard drug solution at three different levels was determined each-day for five days with all solutions being prepared afresh each day. The day-to-day relative standard deviation values were in the range of 1.24-3.26% and represent the best appraisal of repeatability of the proposed methods.

Application

The proposed methods were successfully applied to determine PCPMS in injections. The values obtained by the proposed and the official methods[12]. Which consisted of the measurement of the absorbance of the drug solution in ammonical ethanol at 258 nm, and the results were compared statistically by Student's t-test and F-test and found not to differ significantly. The results are compiled in TABLE 3. Recovery experiments indicated the absence of interference from the commonly encountered pharmaceutical additives and excipients. Both methods are suitable for the determination of PCPMS in pharmaceutical formulations.

TABLE 2: Intra-day accuracy and precision of the methods

Method	PCPMs taken	PCPMs found,*	Range	Relative error, %	SD	RSD, %	ROE, %
Titrimetry	6.0	5.95	0.25	0.84	0.055	0.93	±0.92
	12.0	11.91	0.40	0.78	0.052	0.43	±0.43
	18.0	17.78	0.55	1.22	0.043	0.24	±0.23
Spectrophotometry	5.0	4.92	0.22	1.7	0.062	1.26	±1.25
	15.0	15.89	0.29	0.7	0.265	1.67	±1.66
	25.0	24.61	0.41	1.6	0.391	1.59	±1.58

***Mean value of seven determinations**
In titration method drug taken, found, range and SD are in mg, where as in spectrophotometric method they are in μg/ml,
SD. Standard deviation; RSD. Relative standard deviation and ROE. Range of error at 95% confidence level for six degrees of freedom.

TABLE 3: Results of assay of tablets by the proposed methods

Dosage form and brand name*	Nominal amount, mg/ml	Reference method	Titrimetry	% found*± SD Spectrophotometry
Injection Stemetil	12.5	102.6±1.08	100.5±1.42	101.6±1.83
			t=2.63	t=1.09
			F=1.73	F=2.87

****Marketed value of five determinations**
***Marked by: Nicholas Pharma India Ltd.,**
****Mean value of five determinations. Tabulated value of t at 95% confidence level is 2.77**
Tabulated value of F at 95% confidence level is 6.39

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TABLE 4: Results of recovery study

Method	Formulation Studied	PCPMs in formulation	Pure PCPMs added	Total found	Pure PCPMs recovered %
Titrimetry	Stemetil injection, 12.5 mg/ml	6.03	3.0	9.07	101.3
		6.03	6.0	12.18	102.5
		6.03	12.0	17.74	97.65
Spectrophotometry		101.6	50.0	150.35	97.57
		101.6	100.0	203.20	101.6
		101.6	150.0	257.90	104.2

CONCLUSION

Prochlorperazine has been determined in injections using two different techniques. The developed methods are rapid, simple and accurate. The proposed spectrophotometric method is comparable in sensitivity to many of the existing methods including HPLC procedures. The procedure is free from tedious steps like extraction or heating and involves least number of experimental variables which is reflected in high precision. Both methods are applicable over long dynamic concentration range and can serve as useful reference methods which could be used for a specific prochlorperazine assay.

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