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A validated simple titrimetric method for the quantitative determination of rupatadine as rupatadine fumarate from pharmaceutical dosages

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ABSTRACT

A simple precise, rapid accurate and sensitive titration method was developed for quantitative determination of rupatadine as rupatadine fumarate in pharmaceutical dosage form. The titration was carried out using standardized 0.1 N sodium hydroxide solution. The proposed method was found to be precise with % RSD <1 (n = 6). The method showed strict linearity ($r^2 > 0.99$) between 20 % to 100 % of 100 mg of drug substance weight. The percentage recovery of rupatadine in the optimized method was 98.51 % to 100.269 %. The method is also found to be rugged when checked by different analysts and using different lots of reagents and different laboratories.

KEYWORDS

Rupatadine;
Sodium hydroxide;
Ethanol;
phenolphthalein.

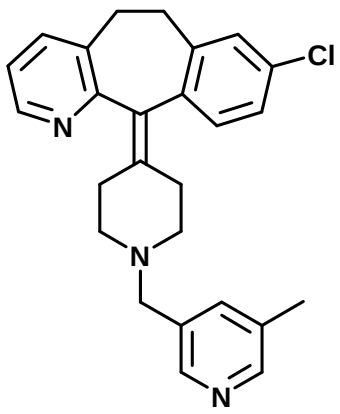
INTRODUCTION

Ruapatadine is 8 chloro 6, 11 dihydro 11-[1-(5 methyl -3-pyridinyl) methyl-4-piperidinylidene]-5 H-benzo [5, 6] cyclohepta [1,2-b] pyridine. It acts as a long acting, non sedative antagonist at histaminergic H_1-receptors and also antagonizes the platelet-activating factor (PAF). Both histamine and PAF cause broncho-constriction and lead to an increase in vascular permeability, acting as a mediator in the inflammatory process, which is responsible for the bronchial hyperactivity.

Quantitative determination of the drug is very important in pharmaceutical quality control and assurance. In the proposed method an attempt has been made to develop a simple titrimetric method for quantitative determination of rupatadine as rupatadine fumarate. The developed titrimetric method was subsequently validated statistically.

This drug is not officially reported in pharmacopeias. In literature survey HPLC[1-3], HPTLC[4] and non-aqueous titration[5] methods were reported.

Structure of rupatadine



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MATERIAL AND METHODS

EXPERIMENTAL

Instrumentation

A Sartorious analytical balance with 0.01 mg was used.

Reagents and chemical

Sodium hydroxide, succinic acid and ethanol of A. R. grade were used.

General procedure

Standardization of 0. 1 N sodium hydroxide solution.

4. 0 g. of sodium hydroxide was transferred in 500 ml of beaker and dissolved in 250 ml of distilled water. It was transferred into 1000 ml of standard volumetric flask and diluted to 1000 ml with distilled water to give concentration as 0.1 N. This solution was standardized by using 0.1 N succinic acid. (0.1 N succinic acid was prepared by dissolving 1.475g. of succinic acid in 250 ml of distilled water). This Standard 0.1 N succinic acid was titrated with 0.1 N sodium hydroxide using 0.01% w/v phenolphthalein indicator until colour of phenolphthalein changes from colorless to pink.

The titration was performed in duplicate.

$$\text{Normality of sodium hydroxide} = \frac{N_1 \times V_1}{V_2}$$

Where N_1 is Normality of standard succinic acid
V_1 is volume of succinic acid
V_2 is burette reading (Volume of sodium hydroxide required for titration)

Quantitative determination of rupatadine

About 0.1 g. of rupatadine as rupatadine fumarate test sample was weighed accurately into a clean and dried titration jar. It was dissolved in 20 ml. analytical grade ethanol. It was titrated with 0.1 N sodium hydroxide solution using 0.01 % w/v phenolphthalein indicator.

Blank determination was also carried out for necessary correction.

One ml of 0.1 N sodium hydroxide is equivalent to 0.013865 g. of rupatadine ($C_{26}H_{26}ClN_3$)

% Rupatadine on the dried basis was calculated as below

$$\% \text{ assay} = \frac{\text{B.R.} \times N \times 0.013865 \times 100}{0.1 \times W}$$

Where B.R. is burette reading in ml at the end point.
N is actual normality of 0.1 N sodium hydroxide.
W is weight of the sample taken in g.

RESULT AND DISCUSSION

Determination of rupatadine

The objective of this work was to determine accurately the content of rupatadine. The assay of rupatadine (on the dried basis) of various batches of rupatadine test sample was analyzed using the above method. It was in the range of 98.51 % to 100.62 %.

Analytical method validation

The method precision was checked after analyzing six different preparations of homogeneous test sample of Rupatadine as rupatadine fumarate. The % RSD of results obtained was found to be 0.7272.

It confirms good precision of the method. The results are presented in TABLE 1.

TABLE 1 : Method of precision

Weight of Rupatadine fumarate in g.	Weight of Rupatadine in g.	Burette reading in ml	Normality of sodium hydroxide	%Assay
0.1279	0.1	7.0	0.1015	98.51
0.1279	0.1	7.05	0.1015	99.21
0.1279	0.1	7.0	0.1015	98.51
0.1279	0.1	7.15	0.1015	100.62
0.1279	0.1	7.1	0.1015	99.91
0.1279	0.1	7.05	0.1015	99.21

Mean of % assay 99.41 %
Standard deviation 0.7814
% RSD 0.7860

Linearity

For the establishment of method linearity, five different weights of rupatadine test samples corresponding to 20 %, 40 %, 60 %, 80 % and 100 % of the about weight (0.1 g.) were taken and analyzed for % of rupatadine content. The results are given in TABLE 2. The titration was conducted once at each level. Calibration curve was drawn by plotting test sample weight in gram on x axis and titre values on y axis.

TABLE 2 : Linearity

Level	Weight of Rupatadine fumarate in g.	Weight of Rupatadine in g.	Burette Reading in ml	Normality of sodium hydroxide	% Assay
1	0.0255	0.020	1.4	0.1015	98.51
2	0.05115	0.040	2.85	0.1015	100.269
3	0.07674	0.060	4.25	0.1015	99.68
4	0.10232	0.080	5.7	0.1015	100.269
5	0.12790	0.100	7.10	0.1015	99.91

Mean of % assay 99.727 %
Standard deviation 0.7253
% RSD 0.7272

The values of correlation coefficient, slope and intercept are given in TABLE 3.

TABLE 3 : Regression values

Correlation coefficient	0.9999
Slope (m)	71.25
Intercept (c)	-0.015
Regression equation	y = 71.25 x – 0.015

Accuracy and recovery

Accuracy was determined at five different levels i.e., 20 %, 40 %, 60 %, 80 % and 100 % of the nominal concentration. (0.1 g.) The titration was conducted in triplicate at each level and the titre value was recorded. The tire value obtained in linearity study was considered as true value during the calculation of percentage (%) recovery. The percentage recovery was calculated using following equation.

$$\text{Percentage recovery} = \frac{\text{Titre value}}{\text{Treu titre value}} \times 100$$

The percentage range recovery of rupatadine was 98.51 to 102.029 %. It confirms the accuracy of the proposed method. (TABLE 4).

Ruggedness

The ruggedness of the method is defined as degree of reproducibility of results obtained by analysis of rupatadine sample under variety of normal test conditions such as different laboratories, different analysts and different lots of reagents. Quantitative determination of rupatadine was conducted on one laboratory. It was again tested in another laboratory using different instrument by different analyst. The assays obtained in two different laboratories were well in agreement. It proved ruggedness of the proposed method.

TABLE 4 : Accuracy and recovery

Level	Weight of Rupatadine fumarate added (g.)	Weight of Rupatadine added (g.)	Weight of Rupatadine found (g.)	% Assay	Mean % assay
1	0.0255	0.020	0.01970	98.51	
	0.0255	0.020	0.02040	102.029	99.680
	0.0255	0.020	0.01970	101.15	
2	0.05115	0.040	0.04010	100.269	
	0.05115	0.040	0.03940	98.51	99.682
	0.05115	0.040	0.04010	100.269	
3	0.07674	0.060	0.05981	99.68	
	0.07674	0.060	0.06051	100.86	100.072
	0.07674	0.060	0.05981	99.68	
4	0.10232	0.080	0.08021	100.269	
	0.10232	0.080	0.07951	99.390	99.970
	0.10232	0.080	0.08021	100.269	
5	0.12785	0.100	0.1006	100.278	
	0.12785	0.100	0.09991	99.910	100.383
	0.12785	0.100	0.1006	100.62	

CONCLUSION

The proposed method of simple titrimetric method was found to be precise, accurate and rugged. The values of percentage recovery and standard deviation showed good sensitivity. The method was completely validated. It showed satisfactory data for all the parameters of validation. This is most simple method as compared to all other methods reported in literature for assay of rupatadine. It requires simple apparatus and less costly chemicals. From validation data it is observed that method is as sensitive as other methods were reported in literature hence it can be used in any analytical laboratory for assay of rupatadine as rupatadine fumarate form its pharmaceutical dosage such as tablets. Hence it can be easily applied for routine quality control application.

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