

DETERMINATION OF RANITIDINE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS BY DIRECT POTENTIOMETRIY

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ABSTRACT

A direct potentiometric titration method was applied for determination of Ranitidine Hydrochloride. The method is based on the treatment of the primary data with nonlinear regression procedure using commercial software. A general formula valid for every type of acid - base titration, derived before is used as a direct input. The acid-base constants of N, N dimethyl-5 - [2-(1-methylamine-2-nitrovinyl) - ethylthiomethyl] furfurylamine hydrochloride were determined by this method in aqueous solutions ($I=0.2$ mol/l KCl) at $t= 25^{\circ}\text{C}$. The obtained pK-values were further used for development of potentiometric method for determination of Ranitidine Hydrochloride in tablets. The validation of the method showed very good accuracy and precision. The present approach can be successfully used in routine analysis of the drug in quality control laboratories.

Keywords: Chemometrics; Potentiometry; Self pH calibration; Acid-Base Constants; Ranitidine Hydrochloride, Validation.

INTRODUCTION

Ranitidine hydrochloride (RNH), chemically N, N dimethyl-5-[2-(1-methylamine-2-nitrovinyl)-ethylthiomethyl] furfurylamine hydrochloride (Figure 1) is a H₂-receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hypersecretory conditions [1]. Although proton pump inhibitors (PPIs) are considered as first line treatment for many conditions associated with gastric hyperacidity, RNH continues to be of great value in combination with PPIs for treating night-time heartburn [2], with antacids for treating mild GERD symptoms [3], and RNH bismuth citrate for treating *Helicobacter pylori* infection [4, 5]. Several approaches are reported for the determination of ranitidine in bulk, pharmaceutical dosage forms, and/or biological fluids. These methods include kinetic spectrophotometry [6, 7], HPLC [8-12], coulometry [13], capillary electrophoresis [14, 15], fluorimetry [16], HPTLC [17], voltammetry [18], potentiometry [19] and polarography [20]. Titrimetric methods with potentiometric [21] and coulometric [13] end-point detection are applied for ranitidine respectively. Potentiometric methods based on ion-selective electrodes [22-24] proposed by various workers, require strict pH control for accurate and precise results.

The dissociation constants of ranitidine are obtained [25] and are widely cited by other authors and referral databases [26].

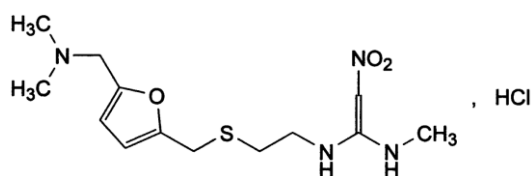


Fig. 1: Chemical structure of ranitidine hydrochloride

This work is based on the earlier developed approach for data processing of potentiometric titration of substances with acid - base properties [27-29]. The proposed approach is based on a system of equations for material balance of the components involved in the acid-base titration. The previously set out general formula (1) and valid for any acid - base titration is quickly solved using the computer program Data Fit.

$$V = V_0 * \left(h - K_w / h + \sum_{m=1}^M \sum_{n=1}^N B_{o,m} * \bar{n}_{H,m} \right) / (C_t - h + K_w / h) \quad (1)$$

Where, V - is volume of the added titrant, ml; V₀ - initial volume of the titrated solution, ml; h - concentration of protons, mol/l; K_w - autoprotolysis constant of water; M - number of components; N - maximum number of protons that a protolyte can accept or release; B_o - concentration of the analyzed base (resp. A_o for acid), mol/l; C_t - total concentration of the titrant, mol/l.

As a result the proton stability acid-basic constants β_n (resp. pK), autoprotolysis constant (K_w) of the water and the concentration of the analysed substance (B₀) are obtained. The most important parameter is the concentration (B₀), which is the analytical result. This study presents the development and validation of an alternative method for the routine analysis of Ranitidine Hydrochloride in the pharmaceutical preparations using direct potentiometry.

MATERIALS AND METHODS

Measurements

The potentiometric titrations were carried in thermostated vessel 25°C, by means of 713 Metrohm pH-meter, equipped with Metrohm combined electrode ref. 6.0228.000 Pt1000 with temperature sensor and auto burette "Radiometer" ABU 80. The ionic strength was supported with KCl ($I = 0.2$ mol/l).

Reagents and solutions

Sodium hydroxide - p.a. and Potassium chloride - p.a. (Merck, Darmstadt, Germany) were used without purification. Ranitidine Hydrochloride standard was obtained from Sigma Aldrich. Tablet formulation containing Ranitidine Hydrochloride 150 mg was obtained commercially. All chemicals investigated, corresponded to p.a. purity and were used without purification.

Sodium hydroxide (0.1 mol/l) in water was prepared by dilution of certified volumetric solutions with carbon-dioxide free redistilled water. The solution of sodium hydroxide was standardized with standard solution of hydrochloric acid.

Preparation of the Standard Solution

Aqueous solution (1.00×10^{-3} mol /l) of Ranitidine Hydrochloride Standard was prepared. The titrant used was a standard solution of sodium hydroxide (0.01 mol/l).

Sample preparation

Procedure for the determination of Ranitidine Hydrochloride

A solution of the analyzed substance at concentration of 1.10^{-2} mol/l and a constant ionic strength 0.2 mol/l was prepared. Aliquot samples of 10.0 ml and 90.0 ml 0.2 mol/l KCl were titrated in a thermo stated glass cell ($25.0 \pm 0.1^{\circ}\text{C}$) with a standard sodium hydroxide solution at concentration of 1.10^{-2} mol/l.

Procedure for the determination of Ranitidine Hydrochloride in tablets

Twenty tablets were weighed accurately and ground into a fine powder. One portion of the powder equivalent to 350 mg of RNH (0.01 mol/l) was accurately weighed into a 100 ml volumetric flask

and extraction was done by shaking for 20 minutes with 40 ml of water, then the volume was diluted to the mark with distilled water, mixed well and filtered using a Whatman No. 42 filter paper. Aliquot samples of 10.0 ml were taken from the filtrate, mixed with 90.0 ml 0.2 mol/l KCl and titrated according to the above described scheme.

RESULTS AND DISCUSSION

The originally proposed procedure was applied to the analysis of Ranitidine Hydrochloride substance. After processing of the

experimental data with the help developed approach, the equilibrium constants and quantitative content were determined. The results of these tests are presented in Table 1.

The results obtained by the two methods show a very close coincidence. Once determined pKa-values can be set as constants in the INPUT at which the calculation time of the analytical results is reduced. Further, in order to validate the method, the procedure was applied for the analysis of synthetic mixtures of the pharmaceutical form of RNH as well as placebo sample.

Table 1: Comparative results of the quantitative determination of Ranitidine Hydrochloride substance by pharmacopoeial method and with the help of the proposed approach

Substance	pKa ₁	pKa ₂	Found,%	Ph.Eur.5
Ranitidine Hydrochloride	2.63	8.32	99.05	99.46

All of the analytical validation parameters for this proposed method were determined according to ICH guidelines [30, 31] as follows:

Selectivity

The proposed method was tested for selectivity by placebo blank and synthetic mixture. A placebo blank containing microcrystalline cellulose, citric acid anhydrous, magnesium stearate, povidone and OY-700 was prepared, extracted and solution made as described under "procedure for tablets". A convenient aliquot of solution was subjected to analysis by titrimetry according to the recommended procedure. It was found that there was no interference between the analyte and placebo.

Accuracy

The accuracy of the proposed method was determined by performing replicate determinations. The intra-day and inter-day variation in the analysis of RNH was measured at three different levels. The accuracy of the analytical method expresses the closeness between the reference value and the found value. Accuracy was evaluated as percentage relative error between the measured and taken amounts/concentrations. The results of this study are compiled in Table 2 and speak of the excellent accuracy of the results.

Table 2: Evaluation of intra-day and inter-day accuracy

RNH taken, mg	Intra-day accuracy			Inter-day accuracy		
	RNH found, mg	RE, %	RSD, %	RNH found, mg	RE, %	RSD, %
37.5	37.39	0.29	0.684	36.96	1.44	1.13
75.0	74.86	0.19	0.245	75.35	0.47	1.06
112.5	113.2	0.62	0.75	111.9	0.53	0.65

Table 3: The results of the Precision analysis of Ranitidine substance and tablets 150 mg

	Substance, %	Tablets, mg
	99.91	150.32
	99.75	149.96
	101.0	150.09
	100.6	150.88
	99.88	149.73
	100.3	150.19
Mean	100.24	150.19
Stand.Deviation	0.488	0.392
Rel.SD,%	0.487	0.261
Conf. Interval	0.511	0.411
% Error	0.523	2.227

Precision

Precision of the method was established by six-time analysis of RNH samples, in substance and tablets. The results obtained are presented in Table 3.

CONCLUSION

The developed and validated potentiometric method is rapid and economic. The statistical parameters and the recovery data reveal good accuracy and precision. Therefore, it is concluded that the proposed method is simple and selective for the determination of RNH in substance and commercial dosage forms. Hence, the present approach can be successfully used in routine analysis of the drug in quality control laboratories.

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