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Research Article

SIX SIMPLE METHODS FOR RANITIDINE HCLDETERMINATION IN BULK AND PHARMACEUTICAL FORMULATIONS BASED ON SPECTROPHOTOMETRY AND POTENTIOMETRY

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ABSTRACT

Six simple, accurate and sensitive methods (A, B, C, D, E, F) for the determination of ranitidine HCl (RHCl) in its bulk sample and in pharmaceutical forms are described. These methods arebased on the drug oxidation by cerium (IV) sulfate. The unreactedCe(IV) was determined by measuring the absorbance decrease of chromotropic acid azo dyes.In caseof methods A-D chromotrope 2B (C2B), arsenazo (I) (Arz(I)), sulfonazo (III) (Sulf(III)) and spadns(Spd) are used. The suitable λ_{max} were 510, 499, 570 and 505 nm for A, B, C and D, respectively. The regression analysis of Beer's plots showed good correlation in the concentration ranges 0.1-2.8, 0.1-2.8, 0.1-2.6 and 0.1-3.0 µg mL^{-1} for A, B, C and D, respectively. For more accurate results, Ringbom optimum concentration ranges were found to be0.4-2.6, 0.5-2.7, 0.2-2.3, 0.4-2.8 µg $mL^{-1}$for methods, respectively. The apparent molar absorptivity, Sandell sensitivity, detection and quantitation limits were calculated. Pure and pharmaceutical forms containing RHCl were analyzed and were tested for the validity of the proposed methods. Method E isbased on the determination of the unreacted Ce(IV) using spectrophotometric titration against Ferrous ammonium sulfate where, the end point was detected spectrophotometrically using Ferrion indicator at 510 nm. Method F was carried out like method E but the end point was detected potentiometrically using Platinum electrode. For the later, The relative standard deviations were ≤ 1.7 with average recoveries 98.2-103.0 %.

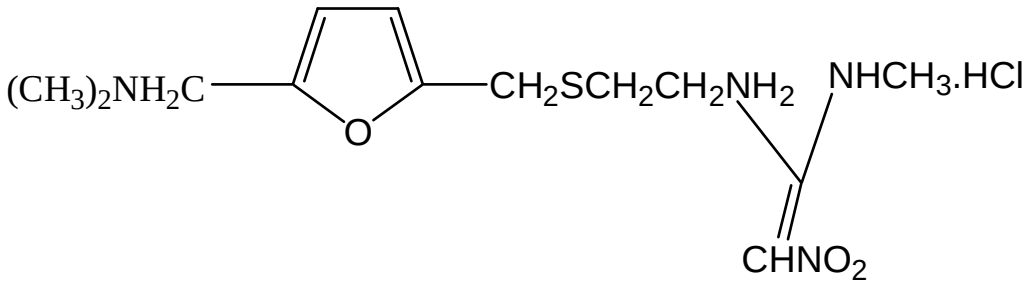
Keywords: Spectrophotometry, Potentiometry, Ranitidine HCl, Oxidation Reduction Reaction.

1. INTRODUCTION

The H_2receptor antagonists(H_2RA)are a class ofdrugsused to block the action of histamine on parietal cells(specifically thehistamine H_2 receptors) in thestomach, decreasing the production ofthe acidby these cells. They are used in the treatment ofdyspepsia, although they have been surpassed in popularity by the more effectiveproton pump inhibitors.The prototypical H_2antagonist was cimetidine, developed by Smith, Kline and French (nowGlaxoSmithKline) in the mid tolate 1960 and first marketed in 1976. The product was sold under the trade name Tagamet®, cimetidine would later become the first everblockbuster drug. The use ofquantitative structure-activity relationships(QSAR) led to the development of other agents starting withRanitidine, first sold as Zantac® which has fewer adverse effectsanddrug interactionsand is more potent[1].

Several methods have been reported for the determination of ranitidine HC1 including chromatography, which is very expensive and sophisticated method[2,3], potentiometry[4,5]. Cerium(IV) sulfate is a versatile oxidimetric reagent. Since its high oxidation potential and excellent solution stability, it was used for the quantitative determination of many drugs[9-11]. This study aims to establish simple colorimetric and potentiometric methods for the determination of RHCl. The structural activity

relationship shows that this oxidative form (S-oxide) is inactive as antipeptic ulcer, for this reason the establishment of methods that quantitatively determine the drug in presence of its oxidized form are of great pharmaceutical value[6-8]. On the other hand, some spectrophotometric methods were applied for the drug dtermination based on ion-pair formation or charge-transfer[12-29].RHCl is Chemically known as, N[2-[[[5-[(dimethylamino)methyl]-2furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethene-diamine,HCl, scheme 1. The empirical formula is $C_{13}H_{22}N_4O_3S$•HCl, representing a molecular weight of 350.87. It is a white to pale yellow, granular substance that is soluble in water,It has a slightly bitter taste and sulfur like odor.



Scheme. 1: Structure formula of Ranitidine HCl

Table 1: Previous methods for determination of RHCl

Previous method	Solvent	$\lambda_{max(nm)}$	Concentration range (µg/mL)	ε (L/mol cm)	Ref.
ceric ammonium sulphate Ce(IV), malachite (MAG)	Sulfuric, water	615	0.4-8.0	1.10×10^4	6
ceric ammonium sulphate, Ce(IV), crystal violet (CV)	Sulfuric, water	582	0.2-1.6	4.09×10^4	6
sodium periodate, crystal violet (CV)	Sulfuric, water	600	400.00-500.00	1.98×103	13
N-bromosuccinimide (NBS), amaranth dye (AM)	Water	520	0.2-3.6	$1.31x10^5$	7
ceric ammonium sulphate Ce(IV),C2R	Sulfuric, water	528	0.1/2.8	$1.91x10^5$	7
Ceric ammonium sulphate Ce(IV), rhodamine 6G (Rh6G)	Sulfuric, water	526	0.1/2.6	$1.74x10^5$	7
Potassium iodate and dichlorofuorescein	Water	520	5-50	$3.88x10^3$	14
Dichromate,diphenylcarbazide	Water	540	5-50	$3.4x10^4$	15
Dichromate,iron(II)	Water	470	5-80	$2.3\ x10^4$	15
Dichromate,orthophenanthroline	Water	510	10-100	$1.2\ x10^4$	15
Ce (IV),p-dimethylaminocinnamaldehyde	perchloric acid, water	464	1-16	$7.13x10^4$	28
p-dimethylaminobenzaldehyde (PDAB)	Hydrochloric acid	503	50-350	$0.311x10^4$	21
Water	Water	313	5-25		22
Bromate, indigo carmine	Water	610	2–12	$2.06 \times l0^4$	25
Bromate, metanil yellow	Water	530	1-7	9.82×10^4	25
p-chloranilic acid (rho-CA)	Acetonitrile	515	20-240	1.052×10^3	29
2,3 dichloro-5,6-dicyanoquinone (DDQ)	Acetone	467	20-140	2.431×10^3	29

2. EXPERIMENTAL

2.1. Apparatus

All the spectral measurements were carried out using a Jenway 6105 UV/Vis single beam spectrophotometer equipped with glass or quartz cells of 1 cm optical path length. A Scientech SA 210 digital balance was used for weighing throughout the study. A water bath (TECCHIN)for heating, potentiometer (Jenway 3010pH meter)for potential measurement.

2.2. MATERIALS

Pure ranitidine HC1 was obtained from GlaxoWellcome, Egypt. Zantac® tablets (GlaxoWellcome Egypt S.A.E. El-Salam City-Cairo-A.R.E.), batch number A508039 labeled to contain 150 mg/tablet, Zantac® injection (GlaxoWellcome), batch number 1320106 labeled to contain 50 mg/ampoule were obtained from local drug store. All chemicals were of analytical grade and double distilled water was used throughout.Arsenazo(I), Sulfonazo(III) and Spandswere obtained from BDH Limited, Poole (England). Chromotrope2B was obtained from alfaAesarGmbh and CoKG (Germany). 1,10phenathroline, ferrous ammonium sulfate hex hydrate and Cerium sulphate tetra hydrate from (sigma-Aldrich).

2.3. Solutions

Ranitidine HCl stock solution was prepared by dissolving an accurately weighed 0.35 g of the pure solid in bidistilled water. The solution was transferred into a 100 mL measuring flask and made up to the mark by bidistilled water to obtain a solution of 1.0×10^{-2} mol L^{-1}. The working standard solutions were obtained by further dilution of stock solution.

Cerium sulphate solution, $5.83x10^{-3}$ mol L^{-1}, was prepared by dissolving accurate weight0.236 g in least amount from 1 mol L^{-1} sulfuric acid, after heating transferred to 50 mL measuringflask and completed to mark by 1 mol L^{-1} sulfuric acid. $1.75x\ 10^{-3}$mol $L^{-1}$was prepared from $5.83x10^{-3}$ by transfer 15 mL in measuring flask 50 mL then completed to mark by 1 mol L^{-1} sulfuric acid. Standard stock solutions of 1×10^{-2} mol $L^{-1}$of C2B, Spd, Arz (I)and sulf (III) were prepared by dissolving accurately weighed 0.2567,0.2852,0.3071 and 0.388 g respectively in bidistilled water and transferred to 50 mL measuring flasks.Ferroin was prepared by dissolving 1,10phenanthroline and Fe(II) in 3:1molar ratio. 0.01molL^{-1}Fe(II) was prepared from ferrous ammonium sulfate hex hydrate by dissolving 0.196 g in bidistilled water in measuring flask, 50 mL. $5x10^{-4}$ mol L^{-1}Fe(II) was prepared by dilution 0.01 mol L^{-1}Solution.

2.4. GENERAL PROCEDURE

2.4.1. Spectrophotometric calibration curves usingchromotrope 2B (A), arsenazo (I) (B), sulfonazo (III) (C) and spadns (D).

For calibration curve construction, solutions containing 0-13µg mL^{-1}RHCl were added to 1.0 mL $1.75x10^{-3}$ mol L^{-1} Ce (IV) solution in 10 mL test tube. After heating these solutions for 5.0 min at 100^0C and then cooling for 3 min a constant concentration of chromtropic acid azo dye was added (0.6, 1.5, 1.6 and 1.5 mL $3.0x10^{-4}$ mol L^{-1} C2B, Spd, Arz(I) andsulf(III) respectively). The content of each tube were quantitatively transferred into 10 mL measuring flask and completed to the mark by 1.0 mol L^{-1} sulfuric acid. The calibration curve was constructed by measuring the decrease in the color at 510, 505, 499, and 570 nm in case of C2B, Spd, Arz (I)and Sulf(III), respectively. The calibration curve was constructed in each case by plotting the concentration of RHCl against the corresponding absorbance at the selected wave length**.**

2.4.2. Spectrophotometric (E)and Potentiometric (F) titration methods

Different volumes from 1.0 $x10^{-4}$mol L^{-1} RHCl(0.0-1.0 mL) were added to 1.0 mL $1.75x10^{-3}$mol L^{-1}, excess volume,Ce(IV). Then it was heated at 100^0C. After cooling, the titration wascarried out against $5.0x10^{-4}$ mol L^{-1} Fe(II) as titrant using ferrion indicator. The absorbance was measured at $\lambda_{max}$of ferrion (510 nm). A titration curve between volume of added Fe(II) on X-axis and absorbance on Y-axis were constructed. The end point was then determined from the extrapolation between two straight lines.The same steps in method E were carried out and the end point was determinedpotentiometrically using platinum electrode as indicator electrode and SCE as reference electrode.

2.4.3. Procedure for pharmaceutical formulation.

Ten Zantac®tablets were weighed, powdered and mixed well into a small dish. A portion equivalent to 200 mg ranitidine HCl was weighed and dissolved in 100mL doubly distilled water. The solution then was shaken well and was filtered through a sintered glass crucible G4. A 1.0 mL aliquot of this solution (2.0 mg mL^{-1}RHCl) was diluted to 100 mL in a calibrated measuring flask. Different aliquots were next subjected to the analysis by using the above describedmethods.In case of ampoules, the content of five ampoules werequantitatively transferred into 250 mL calibrated flask andwere completed to the mark with double distilled water.The above stated methods were applied to determine RHCl concentration.

3. RESULTS AND DISCUSSION

The absorption spectra of the chromotropic acid azo dye, drug, the product of oxidation of the drug with Ce(IV), were constructed in the range 200-800 nm to record the maximum absorbance band at which the measurement will be carried out. The absorption spectra of the drug and that of the product of oxidation of the drug with Ce(IV) do not exhibit any absorption maxima in the visible region. The maximum absorption band were observed at 510,505,499 and 570 nm, respectively for the product of oxidation of the dye with Ce(IV) for methods A-D,Figure (1).

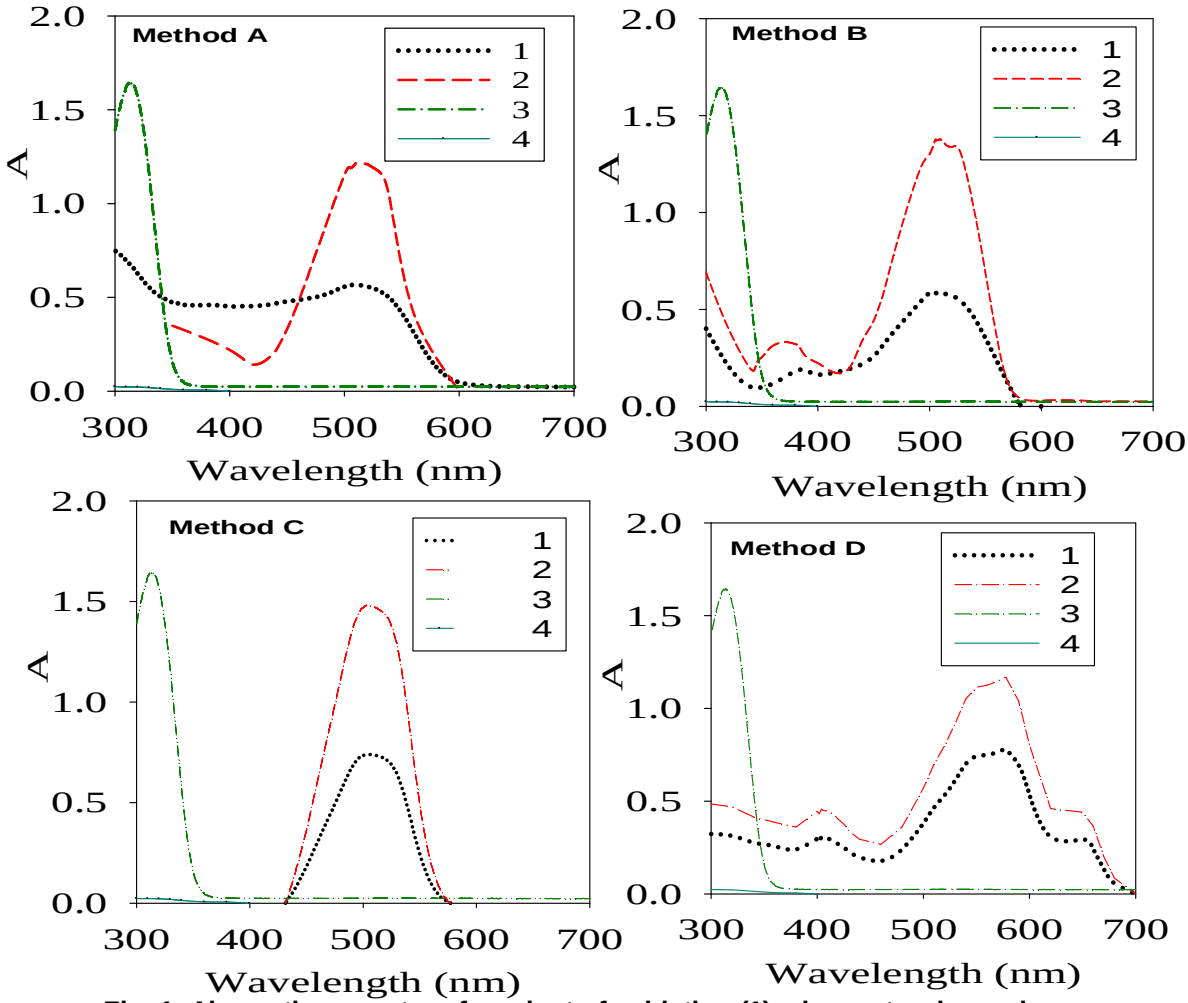


Fig. 1: Absorption spectra of product of oxidation (1), chromotropicazo dye (2), RHCl (3) and Ce(IV)+chromotropicazo dyes (4)

3.1. Spectrophotometric calibration curve

Methods A, B, C and D involved two stages, oxidation of RHCl with excess Ce(IV) solutionin acidmedium under the effect of heating, and determination of the unreacted oxidant by measurement of the decrease in absorbance at 510, 505, 499, and 570 nm for C2B, Spd,Arz(I) and Sulf(III), respectively.

3.1.1 Effect of acid concentration

After several trials, it was found that the most suitable acid to be used with Ce(IV) was 1.0 mL 1.0mol L^{-1} sulfuric acid in the total volume of reaction mixture(10mL).

3.1.2 Effect of temperature and time

Sample solutions containing RHCl, Ce(IV) and H_2SO_4 were heated at different temperatures ranging from 30 to 100^{o}C.The obtained results indicated that the reaction is catalyzed by heating at 100^{o}C for 5 min.

3.1.3 Effect of cooling

Different cooling time was taken in consideration before addition of chromtropicazodyes from 1-5 min. It was found that the solution must be cooled at least for 3 min before addition of chromotropicazodyes.

3.1.4. Molar ratio

Ce(IV) reacts with RHCl with consumption of 25 mol of Ce(IV) per each mole of RHCl, giving a mixture of products. The remaining Ce(IV) reduces the color intensity of C2B, Spd, Arz(I)and Sulf(III) through disruption of the conjugation system in the dye.

3.4. Quantification

3.4.1 Methods A, B, C and D

The calibration curves of the spectrophotometric determination of RHCl using methods A-D, were constructed, Figure 2. Beer's law limits, molar absorptivities, Sandell sensitivities, regression equations and correlation coefficients obtained by the linear squares treatment of the results are given in Table 2. It was shown that methods A-D are validated in mostly the same range, 0.1-2.6 µg mL^{-1}. The molar absorptivity shows the highest value in case of method A using C2B, $1.7x10^5$ L mol^{-1} cm^{-1}.The detection and quantitation limits were calculated from the standard deviation (S.D.) of the absorbance measurements obtained from a series of three blank solutions for each procedure.

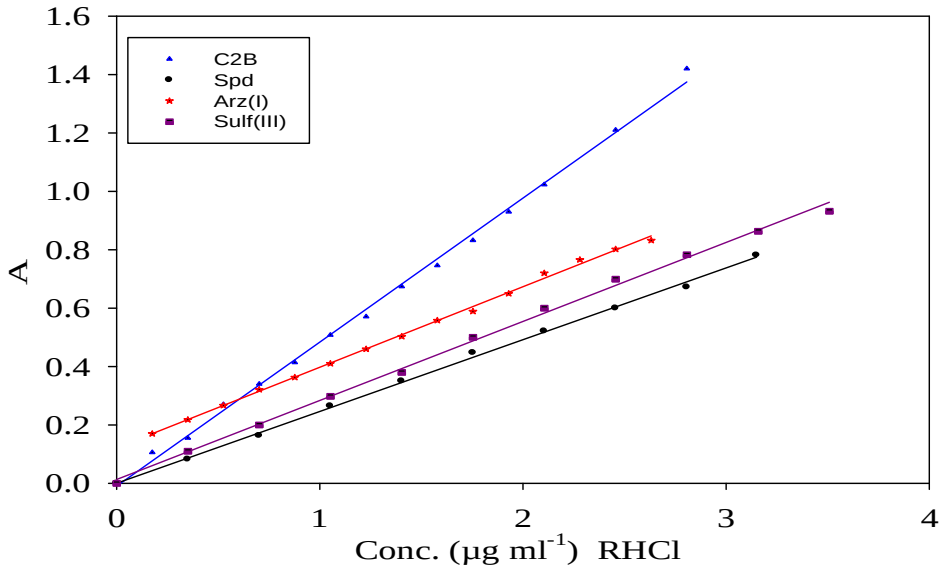


Fig. 2: Calibration curves of determination of RHCl

Table 2: Optical and regression characteristics for Pure ranitidine HCl

	C2B	Sulfoazo(III)	Spadns	Arz(I)
Beer's law limits (µg mL^{-1})	0.1-2.8	0.1-3.0	0.1-2.8	0.1-2.6
Ringbom limits (µg mL^{-1})	0.4-2.6	0.4-2.8	0.5-2.7	0.2-2.3
Molar absorptivity (L mol^{-1} cm^{-1})	$1.7x10^5$	$9.4x10^4$	$8.6x10^4$	$4.6x10^4$
Sandell sensitivity (ng cm^{-2})	2.05	3.7	4.07	7.6
Detection limits (ng mL^{-1})	9.0	11.0	12.0	22.0
Quantitation limits (ng mL^{-1})	29.97	36.63	39.96	73.26
Regression equation				
Slope (a)	0.4877	0.2700	0.2457	0.1310
Intercept (b)	-0.0123	0.0191	0.0004	0.1216
Correlation coefficient	0.9973	0.9981	0.9971	0.9982
SD	0.0046	0.0045	0.006	0.0061
$\lambda_{max(nm)}$	510	570	510	505
SD= the standard deviation				

Table 3: Evaluation of the accuracy and precision of the proposed procedures

Spectrophotometric titration			potentiometric titration		
Taken(µg)	Found(µg)	Recovery±SD%	Taken(µg)	Found(µg)	Recovery±SD%
Pure RHCl					
7.0	7.30	104.3±0.61	10.0	10.0	100.0±0.11
10.0	10.30	103.0±0.65	14.0	14.1	100.7±0.74
14.0	14.20	101.4±0.22	17.5	17.2	98.2±1.17
Zantac ampoule					
7.0	7.50	107.1±0.59	10.0	10.0	100.0±0.43
10.0	10.30	103.0±0.42	14.0	14.0	100.0±0.1.14
14.0	14.00	100.0±0.60	17.5	17.3	98.8±1.11
Zantac tablet					
10.0	10.20	102.0±0.49	10.0	10.0	100.0±0.52
14.0	14.50	103.5±0.60	14.0	14.0	100.0±0.97

Table 4: Determination of RHCl using titrimetric method

Reagent Used	Taken ($\mu g\ ml^{-1}$)	Recovery ±SD%		
		Pure RHCl	Zantac® tablet	Zantac® ampoule
Method A, C2B	1.05	99.20±0.63	98.88±0.11	100.06±0.89
	1.40	100.39±0.38	99.65±0.37	99.00±0.621
	2.10	101.32±0.57	99.33±0.57	100.60±0.57
Method B, Arz(I)	1.05	99.40±0.60	98.37±0.37	99.27±0.65
	1.40	100.10±0.11	100.20±0.34	100.07±0.41
	2.10	100.20±0.08	99.53±0.81	100.47±0.81
Method C, Sulf(III)	1.05	100.22±0.38	99.33±1.15	
	1.40	99.74±0.26	101.31±1.20	103.00±0.58
	2.10	100.20±0.96	101.11±0.96	101.57±0.70
Method D, Spd	1.05	100.64±0.59	100.13±0.22	100.90±0.80
	1.40	100.60±0.44	98.28±0.16	98.38±0.33
	2.10	100.00±0.19	98.33±0.29	99.81±0.19

The limits of detection (K=3) and of quantitation (K=10) were established according to IUPAC definitions[30]. In order to determine the accuracy and precision of the methods, solutions containing three different concentrations of RHCl were prepared and analyzed in six replicates. The analytical results obtained from this investigation are summarized in Table 1. The percentage S.D. was found to be ≤ 1.15,table 3.

3.4.2 Methods E and F

These methods involve the titration of the excess Ce(IV) using Fe(II) followed spectrophotometrically, method E, or potentiometrically, method F. The results show that spectrophotometric titration curve gives asharp inflection for the concentration varied from 7.0-14.0µg of RHCl. Figure 3 shows the spectrophotometric titration curve of 14.0 µg RHCl. It was applied on the pharmaceutical formulations Zantac® tablet and ampoule. The recovery value were found to be in the application range (100.00-108.00%)with RSD values 0.23-0.6%, Table3.In method F, the end point was followed potentiometrically using platinum electrode, the recovery values were 98.20-100.70 % with RSD value 0.1-1.1 table 4, Figure 4.

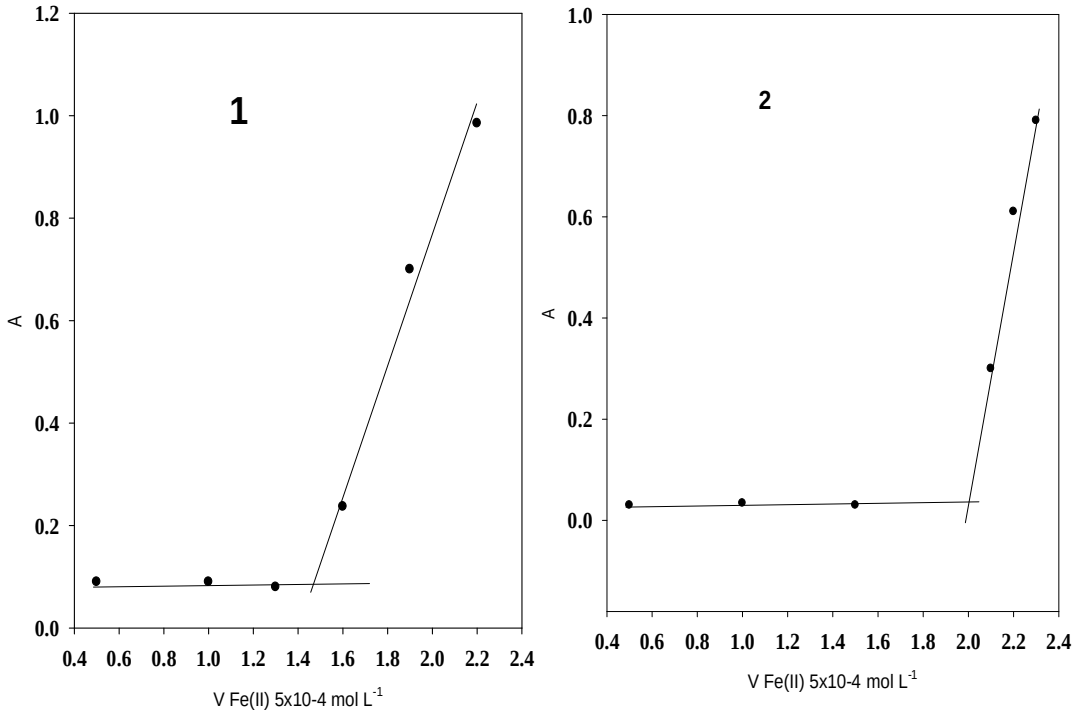


Fig. 3: Spectrophotometric titration 14µg (1)and 10µg RHCl(2) against 5.0×10^{-4}mol L^{-1}Fe(II)

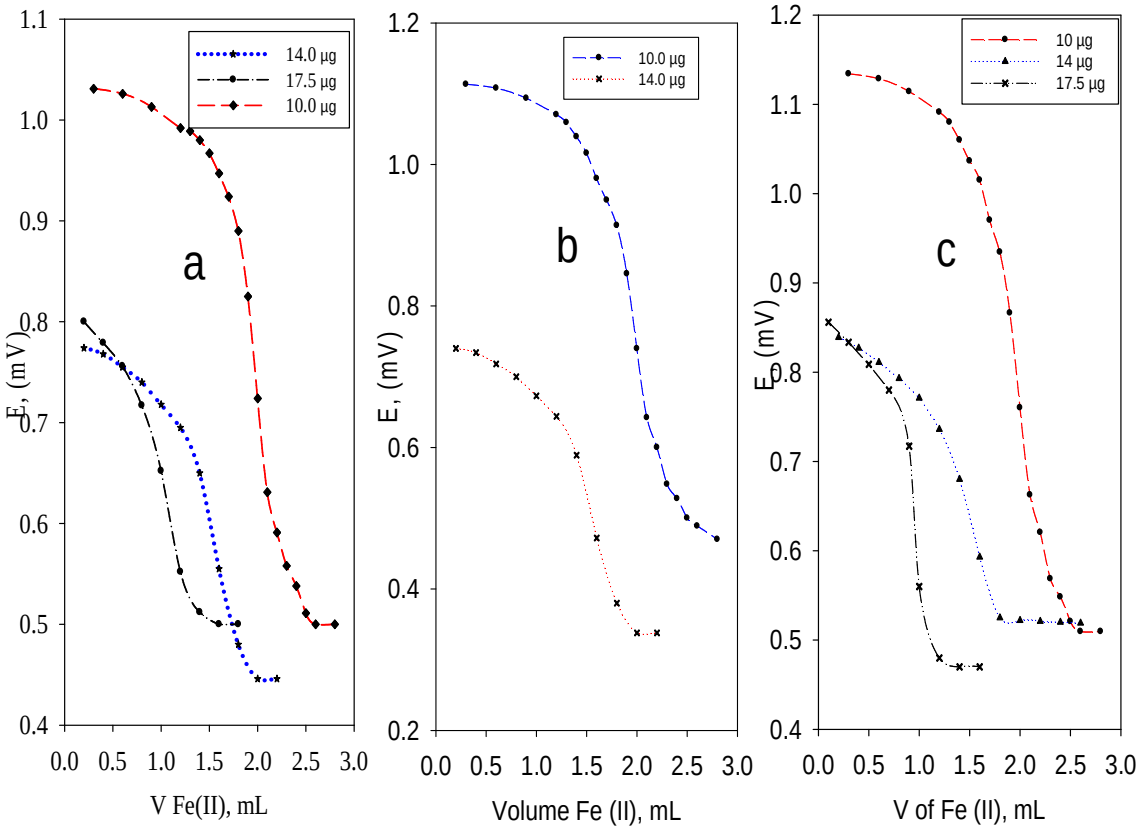


Fig. 4: Potentiometric titration curve of (a) pure RHCl. (b) Zantac®tablet (c) Zantac®ampoule against5.0x10^{-4}molL^{-1}Fe(II)solution.

3.5. Statistcal analysis

The proposed methods were successfully applied to determine RHCl in its dosage forms. The results obtained were compared statistically by Student's t -test (for accuracy) and variance ratio F-test (for precision) with the reference method[31], UV spectrophotometric methods for estimation of ranitidine hydrochloride from tablet formulation. The method obeyed Beer's law and showed good correlation. The results showed that the t- and F- values were less than the critical value indicating that there was no significant difference between the proposed and reference method, table 5. The proposed methods were more accurate with high recoveries than the reference method so the proposed methods can be recommended for routine analysis in the majority of drug quality control laboratories.

Table 5: Statistical treatment of results

Method	Taken	%Recovery ± SD*	t- value	F-value
C2B	1.40	100.39±0.38	2.60	0.43
Arz(I)	1.05	99.40±0.60	4.20	1.20
Sulf(III)	1.05	100.22±0.38	3.12	0.49
Spd	1.05	100.64±0.59	1.70	1.14
Titration ferrion	7.00	103.00±0.61	2.70	1.20
Titration Platinum	10.00	100.00±0.10	1.34	0.23

*Mean ± standard deviation of three replicate analyses

Table 6: Inter– and Intra-days precision of the determination of RHCl using C2B, Arz(I), Sulf(III), ferrion and potentiometric method

		Intra Day			Inter Day
Reagent Used	**Taken ($\mu g\ ml^{-1}$)**	**Found**	**Recovery ±SD%**	**Found**	**Recovery ±SD%**
C2B	1.05	1.04	99.0±0.70	1.03	98.1±1.11
	1.40	1.38	98.5±0.48	1.31	93.5±0.92
Arz(I)	1.05	1.04	99.0±0.63	1.03	98.1±0.93
	1.40	1.35	96.4±0.92	1.38	98.5±0.73
Sulf(III)	1.05	1.03	98.0±0.53	1.04	99.0±0.71
	1.40	1.39	99.2±0.60	1.32	94.3±0.87
Spd	1.05	1.04	99.0±0.83	1.02	97.1±0.98
	1.40	1.33	95.0±0.97	1.39	99.3±1.01
Ferrion	7.00	6.90	98.6±0.57	6.80	97.1±0.45
	10.00	9.87	98.7±0.60	9.80	98.0±0.33
Potentiometric	10.00	9.91	99.1±0.34	9.83	98.3±0.27
	14.00	13.92	99.4±0.55	13.7	97.9±0.43

4. CONCLUSION

The proposed method based on the oxidation of RHCl using Ce(IV) in acidic medium, then the unreacted Ce(IV) was determined. They have advantageous over other reported visible spectrophotometric methods with respect to their higher sensitivity which permits the determination of nano gram amounts, simplicity, reproducibility, precision, accuracy and stability of colored species. The recovery value of the inter and intra-day of the method 95.0-99.4% with RSD% 0.34-0.92% which indicate that these method can be applied for routine analysis and in quality control laboratories for the quantitative determination of the studied drug in raw materials and pharmaceutical formulations.

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